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PSYCHOPHYSIOLOGY AND MEDICAL PSYCHOLOGY

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The Comprehensive Assessment of the Trajectory of Neurocognitive Skills Development in Premature Infants in Longitude

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Abstract

Introduction. This paper aims to give a comprehensive account of differences in the development of cognitive and sensorimotor functions in premature and full-term infants. Prematurity is an important risk factor for neurological and psychomotor disorders, as well as for impaired cognitive development. This study represents a first attempt to conduct a comprehensive assessment using modern instrumental and behavioral methods in a longitudinal perspective.

Methods. The experimental sample was comprised of 42 premature infants (32.4 ± 2.1 weeks of gestation). The control group consisted of 60 full-term infants with typical development and absence of diseases of the central nervous system. The longitudinal study was conducted at 5, 10, 14, and 24 months of age. The participants' eye movements were recorded with the SMI RED 500 eye-tracking system. The Bayley Scales of Infant Development, Third Edition (BSID III) were used to assess cognitive development, receptive and expressive communication skills, as well as gross and fine motor skills.

Results. Compared to the control group premature infants showed significantly lower results by the Bayley cognitive and communicative sub-scales at 5 and 10 months of age, as well as a lag in motor development at 14 and 24 months of age. In addition, the experimental group demonstrated a decrease in the stability and speed of visual attention switching and a lower result in visual search of a simple non-social stimulus at 14 months of age. No significant intergroup differences were found in the perception of social stimuli and the development of joint attention.

Discussion. Prematurity selectively influences the development of neurocognitive functions. The outcomes of prematurity partially disappear by the end of the second year of life.

Keywords

cognitive development, attention, motor development, communicative development, visual perception, prematurity, infancy, early childhood, Bailey Scales, eye tracking

Highlights

► Premature infants demonstrate a developmental lag in cognitive and speech functions during in infancy and a developmental lag in motor skills in the second year of life.

► The level of development of involuntary attention decreases significantly in premature infants at 14 months of age.

► Premature and full-term infants do not differ in their abilities for perceiving social information.

► The outcomes of prematurity partially disappear by the end of the second year of life.

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Introduction

The periods of infancy and early childhood are characterized by the most intensive development of the organism and its adaptation to the environment. In early childhood children are characterized by a number of significant new formations in cognitive and sensorimotor spheres, which include the main components of thinking, motor functioning, sensory perception, speech, and socio-emotional skills (Baranov, Maslova, & Namazova-Baranova, 2012). At the same time, the pace and characteristics of the development of children in these ontogenetic periods depends entirely upon biological risk factors and environmental impacts (Belousova, Prusakov, & Utkuzova, 2009; Weijer-Bergsma, Wijnroks, & Jongmans, 2008). Prematurity is one of such risk factors (Safina, Volyanyuk, Potapova, & Fisheleva, 2018).

Today, there is a significant increase in the number of children born prematurely, which is associated with the development of intensive care technologies for newborns and a significant increase in the survival rate for children with low and extremely low birth weight. According to the most recent statistics, the rate of preterm birth varies from 5 to 18% of the total number of newborns in 184 countries. According to Russian official data, the survival rate for children weighing less than 1000 g at birth is about 85% (Safina et al., 2018). Moreover, this category of patients is the main risk group for neurological and psychomotor abnormalities, including those leading to disability (Safina et al., 2018; Filkina, Dolotova, Andreiuk, & Vorobeva, 2010; Barkun, Lysenko, Zhuravleva, Kosenkova, & Buchkina, 2013; Dolinina, Gromova, & Kopylova, 2014). In numerous clinical studies, prematurity is considered to be a factor in the formation of cerebral palsy (Namazova-Baranova et al., 2016), autism (Hofheimer, Sheinkopf, & Eyler, 2014; Elsabbagh et al., 2009) and attention-deficit/hyperactivity disorder (Franz et al., 2018).

However, atypical development in cognitive and psychomotor spheres is often observed even in somatically healthy infants with mild and moderate degree of prematurity (gestational age < 28 weeks, body weight at birth < 1500 g) (Emberson, Boldin, Riccio, Guillet, & Aslin, 2017; Blencowe et al., 2012). A large amount of data indicates various disorders in the development of cognitive functions in premature infants, including an increased risk of attention and memory deficits, as well as deficits in information processing speed and executive functions (Emberson et al., 2017; Ross-Sheehy, Perone, Macek, & Eschman, 2017; Ionio et al., 2016; Oudgenoeg-Paz, Mulder, Jongmans, van der Ham, & Van der Stigchel, 2017; Yaari et al., 2018; Zmij, Witt, Weitkämper, Neumann, & Lücke, 2017; Williamson & Jakobson, 2014). Many researchers also note that compared to children with normative development, those born prematurely are at increased risk of motor impairments (Oudgenoeg-Paz et al., 2017; Yaari et al., 2018; Geldof et al., 2016; Zuccarini et al., 2018; You, Shamsi, Hao, Cao, & Yang, 2019; Kaul et al., 2019; Peyton, Schreiber, & Msall, 2018).

The issue of the development of visual functions and the perception of visual information in premature children remains much less studied. Meanwhile, this aspect seems to be important for studying, as the pace and characteristics of the development of visual perception in infancy are undoubtedly associated with the subsequent neurocognitive development of children.

It is known that since the first months of life children have a general tendency to focus on faces and stimuli similar to faces (Konishi Yukihiko et al., 2012; Beier, & Spelke, 2012). The preference for social stimuli in infancy is considered by researchers as an indicator of the further development of social skills (e. i. following another person's gaze of another person and joint attention) (Imafuku et al., 2017). In turn, many researchers recognized that the development of joint attention by the second year of life is as a reliable predictor for speech development in younger and older preschool children (De Schuymer, Groote, Desoete, & Roeyers, 2012; Frischen, Bayliss, & Tipper, 2007; Tomasello, Carpenter, & Lizkowski, 2007). It was found that the frequency of initiating joint attention in infants is associated with speech acquisition, information processing, as well as with individual differences in intelligence and social competencies (Van Hecke et al., 2007).

Eye-tracking is the method for recording and analyzing eye movements that is used for the assessment of visual perception. This method is one of the most widespread for the study of cognitive processes in infants, as it does not require a verbal response from respondents and has high reliability in repeated testing in this age group (Navab, Gillespie-Lynch, Johnson, Sigman, & Hutman, 2012).

Infants start to demonstrate cortical control when switching attention from one visual object to another since 4 months of age. Thus, the characteristics of the subjects' fixation on stimuli may be considered as effective early indicator of attention disorders and impairments of cortical structures associated with atypical development resulting from prematurity (Atkinson & Braddick, 2012). As previous studies have suggested, premature infants or those with low birth weight are at increased risk of impaired perception and recognition of faces (De Schuymer et al., 2012; Telford et al., 2016; Perez-Roche et al., 2017). In the work of E. J. Telford et al. the authors report that compared to infants from a normative group the premature ones spent significantly more time examining the social content of stimuli (Telford et al., 2016). The findings of L. De Schuymer et al. demonstrate that compared to full-term infants their premature peers more often and for a longer time break eye contact with their parents by gaze aversion (De Schuymer et al., 2012).

However, despite numerous studies on deviations associated with premature birth, the results on the outcomes of neurocognitive development in such children are heterogeneous. The literature describes that early exposure to the external environment can both cause harm and become an advantage for the development of the nervous system (Ionio et al., 2016; Peña, Arias, & Dehaene-Lambertz, 2014; Vandormael, Schoenhals, Hüppi, Filippa, & Tolsa, 2019).

Thus, identifying the characteristics of cognitive and socio-communicative development of premature infants in infancy and early childhood is an important issue. An early assessment of oculomotor activity and various components of visual attention seems promising for predicting rates of maturation of mental functions in normative and deviant child development.

In this paper, we have turned our attention to studying the differences in the level of development of cognitive and sensorimotor functions in premature and full-term infants.

This study represents a first attempt to conduct comprehensive longitudinal study using modern instrumental and behavioral methods in the Russian sample of premature and normally developing infants and children. For the first time, the Bayley Scales of Infant Development, Third Edition (BSID III) was tested in a sample of Russian-speaking children. We compared the results obtained in our study with those of previously published data.

Methods

Sample characteristics

The study was conducted in the Laboratory for Brain and Neurocognitive Development, Ural Federal University named after first President of Russia B.N. Yeltsin.

The experimental sample was comprised of 42 premature infants, 22 of whom were boys (32.4 ± 2.1 weeks of gestation, 1614 ± 406 g average birth weight).

The subjects were recruited from the City Perinatal Center in Yekaterinburg.

The experimental sample was comprised of 42 premature infants (22 boys and 20 girls, 32.4 ± 2.1 weeks of gestation, 1614 ± 406 g average birth weight).

Criteria for inclusion in the experimental group: prematurity at 28–36 weeks of age, body weight of at least 1.0 kg, absence of malformations of the brain, heart, and other organs, absence of cerebral haemorrhages or hypoxic foci of any localization and degree according to the results of neurosonography, absence of neonatal hyperbilirubinemia, and absence of confirmed intrauterine infection.

The control group consisted of 60 full-term infants (40 boys and 20 girls) with typical development and absence of diseases of the central nervous system.

We obtained signed informed consent for examination and personal data processing from parents of each child involved in our study. The study design was approved by the Local Ethics Committee of the Ministry of Health of Russia (protocol no. 1, February 20, 2015).

The longitudinal study was conducted at 5, 10, 14 and 24 months of age (± 2 weeks in each longitudinal test).

According to the literature, in most cases the development of 2-year-old prematurely born infants meets the developmental criteria for their corrected age (Lebedeva, Nevryuzina, & Frolova, 2011; Harel-Gadassi et al., 2018). Thus, the subjects were unified by their corrected age (the difference between the actual age and the weeks of prematurity).

Some of the subjects were withdrawn from the study after the request of their parents or by other circumstances. The criteria for inclusion of subjects in the statistical analysis were the presence of eye-movement recordings in each longitudinal test and the sufficient quality of the obtained data. Table 1demonstrates the total of subjects and age characteristics of the groups.

Table 1

Age characteristics of the groups

Longitudinal test	Subjects (n)	Mean chronological age (months), m ± SD	Mean corrected age (months), m ± SD
		Control group	
5 months	17 (м = 9)	5,89 ± 0,78	–
10 months	29 (м = 16)	10,50 ± 0,22	–
14 months	36 (м = 20)	14,89 ± 1,05	–
24 months	19 (м = 12)	24,68 ± 0,62	–
		Experimental group	
5 months	9 (м = 5)	6,23 ± 0,82	5,85 ± 0,77
10 months	18 (м = 10)	11,92 ± 0,63	10,34 ± 0,52
14 months	22 (м = 13)	15,20 ± 1,22	14,48 ± 0,93
24 months	11 (м = 6)	25,19 ± 1,23	24,68 ± 0,84

Note: m – number of boys

The Bayley Scales of Infant Development, Third Edition (BSID III)

The Beyley Scales of Infant Development is the most widely used technique for assessing the early development of neurocognitive functions in early childhood. In 1969 this technique was developed by Nancy Bailey together with her colleagues at the University of Berkeley; it was intended for diagnosing children aged 1 to 42 months (Bayley, 2006). In this work, we used its third edition, revised and approved in 2008, which includes three subscales of the mental scale(cognitive subscale, expressive subscale, and receptive communication)and two subscales of the psychomotor scale (gross and fine motor skills).

Each subscale had a fixed number of tasks and items used to assess each particular skill. The experimenter can independently choose the order of the tests, depending on children's' temperament, his/her interest in performing certain tasks, as well as on the degree of contact. The variability of the order of the tests allowed us to obtain an adequate idea of different aspects of the development of the child.

Eye-Movement Recording Method

In this work, we used the SMI RED 500 eye-tracking system representing a non-contact, remotely controlled infrared camera that automatically tracks eye movements. During the experiment, the infant sat on the parent's lap or alone in the car seat. The location of the eye-tracker system was corrected so that the middle of the monitor was at the same height with the child's eyes at a distance of 60–70 cm.

Stimulus materials were provided by a research group from the Center for Brain and Cognitive Development (Birkbeck, University of London, UK), where experimental procedures for the development of infants were developed and tested as a part of the European project for the study of risk factors for autism spectrum disorders (ASD) and attention deficit/hyperactivity disorder (ADHD).

The stimulus materials included the following three blocks:

1) 8 pictures with five different objects, one of which represented the image of a person's face (a social stimulus). The other four objects were distractors and represented non-social stimuli: a bird, a car, a phone, and a blurred face image. Similar tests were used in the work of Telford et al. (2016).

2) 16 pictures including seven identical stimuli and a differing one. The identical (irrelevant) stimuli represented a diagonal cross; the differing (relevant) stimuli represented a circle in simple tests and a vertical cross in complex ones.

3) 6 videos representing three objects: a model (woman) and two toys. The model sits with her head down, then raises her head and attracts the attention of the child, looking straight ahead and raising her eyebrows; then she looks at one of the toys, which is a relevant stimulus in this case. Similar trials were used by Senju & Csibra (2008).

To calculate the number of trials performed by each subject we used certain criteria. In the first block, the test was considered performed if the first fixation of the child's gaze was in the face area. In the second block, to perform the test it was necessary to find a different object. In other words, we assessed the presence of fixations in the area of a relevant stimulus. In the third block, the child was considered to look away from the relevant stimulus.

Statistical processing

To assess the differences between the groups of subjects we used the Mann-Whitney test. The analysis was carried out according to the following variables:

1) "raw" scores for 5 Bayley-III subscales: cognitive communication (CogRaw), receptive communication (RecRaw), expressive communication (ExpRaw), gross (GmRaw) motor skills, and fine motor skills (FmRaw).

2) Block 1: the number of valid (VT) and performed tests (CompT), the duration of fixations (ms) on the images of a face (faceFD), a blurred face image (noiseFD), a bird (birdFD), a car (carFD), and a phone (phoneFD).

3) Block 2: the number of valid test (VT); performed 'simple' (CompO) and 'complex' (CompPl) tests; time of reaction (ms) to distractors (DisRT), a circle (ORT), and a vertical cross (PlRT).

4) Block 3: the number of valid tests (VT), the number of tests with the first gaze at relevant (Rel) and irrelevant (Unrl) stimuli, the duration of gazing (ms) relevant (RelFD) and irrelevant (UnrlFD) stimuli.

The calculations were performed using the IBM SPSS Statistics 22 software for Windows.

Results

Table 2 presents the results of statistical analysis to assess differences in the development of neurocognitive functions in a sample of full-term and premature infants.

There are intergroup trend differences in the first longitudinal trial by two subscales: cognitive development and receptive communication. At the age of 5 months, neurologically healthy infants had higher scores in comparison with premature infants both in the cognitive subscale (29.12 ± 3.53 vs 25.80 ± 2.16) and in recessive communication (9.71 ± 1.40 vs 8.00 ± 0.70).

In the second longitudinal trial we observed significant differences in three subscales: cognitive development (39.41 ± 4.06 vs 36.40 ± 4.06), receptive communication (13.71 ± 2.05 vs 11.60 ± 1.89), and gross motor skills (39.88 ± 3.30 vs 35.33 ± 3.96).

Table 2

U-test for Bayley Scales

Longitudinal tests	Means, significance level (U-test)				
	CogRaw	RecRaw	ExpRaw	FmRaw	GmRaw
5 months	**18.5;0.06***	**10.5;0.01****	26.0;0.18	22.5;0.11	26.5;0.21
10 months	**160.5;0.04****	**119.5;0.003****	**176.5;0.08***	190.5;0.16	**98.5;0.001****
14 months	276.0;0.56	253.0;0.31	237.0;0.17	**208.5;0.06***	**191.0;0.03****
24 months	39.0;0,11	41.5;0,15	45.0; 0,20	58.0;0.62	**32.0;0.04****

Note: ** – significant differences *($p < 0.05$)*,* – trend differences *($p < 0.1$)*

At the age of 14 months, the subjects demonstrated pronounced differences only in the field of motor development. According to the subscale of fine motor skills, healthy subjects scored higher than premature infants (33.56 ± 2.95 vs 31.83 ± 2.72). Similar results were obtained when evaluating gross motor skills (49.14 ± 2.90 vs 46.78 ± 4.32).

Finally, at the last longitudinal trial the only differences we observed were those in large motor skills. The actual level of motor skills in the control group was significantly higher than that observed in the experimental one (59.74 ± 4.01 vs 56.42 ± 2.37).

Table 3 presents intergroup differences in the trials of the first block of the experiment measured by eye-tracking.

We observed significant differences in the number of valid trials among subjects aged 14 months. Thus, in the first block normative children had statistically more valid trials compared with premature infants (6.33 ± 1.51 vs 5.50 ± 1.82).

In addition, significant intergroup differences were found in the duration of gazing the images of birds in subjects aged 10 months (690.97 ± 289.06 ms in full-term infants, 281.85 ± 129.99 ms in premature infants), as well as in the duration of gazing the telephone images in subjects aged 14 months (630.46 ± 377.86 ms vs 330.59 ± 149.58 ms, full-term and premature subjects, respectively).

Table 3
U-test for the first block of stimuli for eye-tracker

Longitudinal tests	Means, significance level (U-test)						
	VT	CompT	faceFD	noiseFD	birdFD	carDF	phoneFD
5 months	39.0; 0.78	39.0;0.78	37.0;0.67	33.0;0.45	37.5; 0.69	30.0; 0.33	32.0; 0.41
10 months	248.5; 0.62	199.5; 0.13	245.0; 0.57	242.0; 0.53	**126.0; 0.002****	215.0; 0.24	246.0; 0.58
14 months	**207.0; 0.04****	277,0; 0,48	306.0; 0.87	**218.0; 0.07***	308.0; 0.90	260.0; 0.32	**182.5; 0.014****
24 months	68.0; 0.65	62.0; 0.45	60.0; 0.396	74.0; 0.91	69.0; 0.71	65.0; 0.56	56.0; 0,28

Note: ** – significant differences *($p < 0.05$)*,* – trend differences *($p < 0.1$)*

Table 4 presents intergroup differences in the trials of the second block for eye-tracker.

Table 4
U-test for the second block of stimuli for eye-tracker

Longitudinal tests	Means, significance level (U-test)					
	VT	CompO	CompPI	DisRT	ORT	PIRT
5 months	26.5; 0,373	34.0; 0.84	31.0; 0.63	29.0; 0.51	25.0; 0.30	30.0; 0.76
10 months	156.5; 0.19	213.5; 0.78	221.0; 0.92	183.0; 0.31	151.0; 0.38	91.0; 0.55
14 months	245.5; 0.48	**190.5; 0.057***	244.0; 0.45	**157.0; 0.011****	202.0; 0.18	219.00; 0.90
24 months	67.0; 0.81	58.0; 0.43	50.5; 0.22	72.0; 1.00	66.0; 0.91	27.00; 0.46

Note: ** – significant differences *($p < 0.05$)*,* – trend differences *($p < 0.1$)*

We obtained significant differences in the response time to distractors in subjects at 14 months (658.25 ± 118.37 ms versus 772.61 ± 165.46 ms, normative and premature infants, respectively). In this case the reaction time is the period from the beginning of the presentation of the trial or the change in the stimulus to the end of a saccade towards the target or distractor (measured in milliseconds). Compared to prematurely born children, normatively developing ones reacted more quickly to the presentation and switching of stimuli at the age of 14 months.

Moreover, there were trend differences in the number of "simple" trials between groups. In most cases, normative children found a differing stimulus of round form compared to premature infants (6.85 ± 1.26 versus 4.43 ± 0.81).

Table 5 demonstrates differences in the performance of trials from the third block for eye-tracker.

Table 5
U-test for the third block of stimuli for eye-tracker

Longitudinal tests	Means, significance level (U-test)				
	VT	Rel	Unrl	RelFD	UnrlFD
10 months	45.0; 0.22	55.5; 0.65	60.0; 0.85	61.0; 0.907	61.0; 0.907
14 months	137.5; 0,65	142.5; 0.84	119.5; 0.32	108.0; 0.19	**75.0; 0.018****
24 months	84.0; 0.13	92.5; 0.35	116.0; 0.97	101.0; 0.55	96.0; 0.42

Note: ** – significant differences *($p < 0.05$)*,* – trend differences *($p < 0.1$)*

According to this block, significant intergroup differences in the duration of gazing an irrelevant object were observed at the age of 14 months. Compared to the experimental group, the children from the control group fixed their gaze at incongruent stimuli for a longer time (1112.26 ± 429.01 ms vs 750.83 ± 328.02 ms full-term and premature infants, respectively).

Discussion

Statistical processing of the data obtained using the Bayley Scales of Infant Development, Third Edition (BSID III) clearly shows the dynamics of the development of various neurocognitive functions in premature infants compared to the normative sample. There is a lag in mental and socio-communicative development during the first year of the postnatal period of ontogenesis in children born prematurely. However, by the end of the second year of life, the intergroup differences in the level of formation of cognitive and communicative skills disappear.

The data obtained are consistent with previous studies suggesting that premature infants have an increased risk of speech disorders, in particular, speech perception, which may be associated with delayed maturation of neural pathways and morphofunctional immaturity of certain structures of the cerebral cortex (Adams-Chapman, Bann, & Vaucher, 2013; Torras-Mañá, Guillamón-Valenzuela, Ramírez-Mallafré, Brun-Gasca, & Fornieles-Deu, 2014; Velikos et al., 2015).

The absence of significant differences in the groups in the subscales of gross and fine motor skills in the first year of life and also differences in these parameters in the next two longitudinal tests do not find unambiguous literary confirmation, which may be presumably explained by the characteristics of the sample and the characteristic of the research technique.

In this study the analysis of visual search was carried out in the context of the pop-out paradigm (Gliga, Elsabbagh, Andravizou, & Johnson, 2009). According to this research paradigm, the time spent by the target stimulus does not depend on the number of distracting objects (distractors), because it differs significantly from distractors due to the presence of a unique perceptual trait, such as color, shape, or spatial arrangement. In this case, the detection of a visual stimulus is determined by the mechanisms of involuntary attention and information processing by the primary regions of the visual cortex.

Differences in the number of valid trials in the first block show that at 14 months of age children from the control group demonstrated higher stability in the duration of gazing the images. Meanwhile premature subjects demonstrated higher exhaustion of attention. We also observe no significant differences in this parameter in other longitudinal tests, which demonstrates a kind of "failure" in the development of involuntary visual attention in children born prematurely. This may be explained by the myelination of neural pathways in the frontal visual region that controls oculomotor behavior in children with this perinatal pathology (Atkinson & Braddick, 2012). The characteristics of the development of attention span in preterm infants are confirmed by the data obtained from the second visual search test for eye-tracker.

As mentioned above, the ability to visually perceive social information during infancy plays an important role in the further development of a child's communicative and speech skills.

Conclusions

1. At 5 months, premature infants showed a lower level of development of cognitive skills and receptive communication compared with their healthy peers.
2. At 10 months years of age, premature infants showed lower results by the subscales of cognitive development, receptive and expressive communication, as well as in gross motor skills.
3. At 14 months years of age, premature infants showed lower developmental rates in fine and gross motor skills, a decrease in the stability and speed of switching of visual attention, as well as lower results in the visual search for a simple non-social stimulus.
4. At 2 years of age, children with prematurity demonstrated a lower level of development of gross motor skills compared with normatively developing children.

Thus, it is obvious that the influence of prematurity on the rate of formation of visual attention and also cognitive and communicative skills partially disappear by the end of the second year of life.

Nevertheless, from the first days of their life children born prematurely require extraordinary attention, as well as clinical and psycho-preventive measures, aimed at maintaining their somatic and neuropsychiatric well-being.

Aknowlegments

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The electroencephalographic correlate of cognitive deficiency at the children who had got over a perinatal arterial ischemic stroke

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Abstract

Introduction. It is designated relevance of singling out of the effective electroencephalographic range reflecting cognitive deficiency at the children who had a perinatal ischemic stroke. It is necessary for the subsequent search for early markers of possible cognitive disturbances in later years. The scientific novelty of the study is in attempt of singling out of a neurophysiological correlate of cognitive deficiency at children with rare pathology of the central nervous system with use of the integrated approach including behavioral and equipment-specific methods.

Methods. In the section it is described peculiarities of using electroencephalographic techniques and Bayley-III scales for selection of a neurophysiological correlate of cognitive deficiency in the babyhood and childhood.

Results. The section includes data of statistical processing of a cognitive subscale of the Bailey-III technique and the analysis of the rescaled density of power spectrum of electroencephalographic ranges: beta2 (17–30 Hz) and gamma (30–40 Hz) in projections of prefrontal cortex. The beta2-band showed the greatest ratios with the indicators of the used subscale.

Results and discussion.

It is considered reasons of separation of the children with perinatal arterial ischemic strokes in a group of the high risk of the cognitive disfunction which can develop in course of time. We conclude about a possibility of singling out of beta2-band as the most effective indicator for a neurophysiological correlate of cognitive deficiency at the children who had a perinatal arterial ischemic stroke.

Keywords

babyhood, childhood, perinatal blood-stroke, ischemic stroke, neurophysiological correlates, cognitive deficiency, electroencephalography, Bayley-III scales, beta activity, gamma activity

Highlights

► neurophysiological correlates of cognitive deficiency at children can have some specificity depending on character and time of damage;
► this correlate can make a contribution to further work in search of early markers of cognitive defects at the children having got over a perinatal arterial ischemic stroke and who can progress in later years;
► electroencephalographic beta2 band can be considered as the most effective indicator reflecting cognitive deficiency at the children who had a perinatal arterial ischemic stroke.

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Introduction

The Perinatal Arterial Ischemic Stroke (PAIS) is a local cerebrovascular disturbance caused by thrombosis or embolism during the period between the 20th week of the antenatal life and the 28th day of postnatal period, with the subsequent formation of a local infarction of brain tissue [Fluss, Dinomais & Chabrier, 2019].

Pathology occurrence varies from 1/1600 to 1/5000 according to publications, it is supposed that a part of PAIS cases remain underdiagnosed, in connection with the features of suggestive clinical findings in the neonatal period [Narogan et al., 2019]. The number of children with this pathology increases. It's not so long ago that even the stroke which occurred in infancy was considered as a rarity [Lvova, Kuznetsov, Gusev & Volkhina, 2013].

The perinatal stroke is distinguished as one of the causes of possible forming of the infants' expressed cognitive defects which can worsen over the years [Ilves et al., 2016]. However, using the early markers for identification of high risk group allowing to prove additional therapeutic correction are under discussion at the moment.

The results of the meta-study devoted to the selection of early markers of cognitive defects at the infants revealed that characteristics of background activity of the electroencephalogram (EEG) can be effective for these purposes, however the obtained data were too heterogeneous [Kong et al., 2018].

The variability of indicators is very likely caused by restriction of the possibility of selection of area of interest since the substrates making a contribution to work of cognitive functions, as we know, have not only cortical location [Filley, 2019]. Also, perhaps, features of the studied clinical groups and the nature of cerebral affection exert an impact.

Further work in this direction requires separation of the possible neurophysiological correlate assisting designation of effective EEG-range which will reflect cognitive deficiency at children with PAIS.

Methods

The research was conducted on the basis of the testing laboratory of the brain and neurocognitive development at the Department of psychology in the Ural Federal University named after the first President of Russia B.N. Yeltsin.

Within the case control two groups were formed.

The criteria of inclusion of the participants in the group of control: typically developmental near term infant (37–42 weeks) with the anthropometric measures corresponding to a framework of the physiological norm characterized by absence of significant neurologic and somatic pathologies both at birth and throughout all research period.

The criteria of inclusion of the participants in the experimental group: carried to full time infants with the anthropometric measures at birth which are within the physiological norm, had got over the ischemic stroke (IS) in the mesencephalic artery district during the perinatal life (the brain stroke was confirmed with help of magnetic resonance brain imaging); lack of intracraneal hemorrhages and symmetric periventricular of the ischemic foci. The data of the participants of congenital cardiac event, which was the indication for surgical cardiac interference, as well as the participants of symptomatic epilepsy were rejected.

All the research subjects underwent inspection every other small periods of time. The first stage was carried out in 5 months, then the research procedure was repeated in 10, 14 and 24 months.

These age specific points were selected taking into account:

1. Periodization of the rehabilitation periods of the cerebral thrombosis [Clinical recommendations… , 2013]:

an early recovery period (up to 6 months after the event): point of 5 months;

the late recovery period (up to 2 years after the event): in connection with its duration two points were included – 10 and 14 months;

24 months: it is the point that completes the late recovery period and which is characterized by the end of the most active recovery processes. That fact allows to evaluate fate even at this stage, being guided by the experience of other authors in research of the early diagnostics [Jaillard et al., 2003; Pierrat et al., 2017].

2. "Critical" stages of neurophysiological development of typically developmental children [Marshall, Bar-Haim & Fox, 2002].

68 infants of the control group and 16 infants of the experimental group participated in the research.

The research procedure included the following stages for each participant:

1. Legal representatives of the research subjects carried out giving the voluntary informed consent to participation in the research project.
2. For creation of the greatest homogeneity of the groups under study the form specifying sociodemographic family status was completed by the parents.
3. Conduct of the technique of "Beyley Scales of Infant Development" (Bailey-III).
4. For signal recording of cerebral bioelectrical activity of research subjects the multichannel (128 assignments) electroencephalographic system of the expert class GEODESIC EEG SYSTEM 300 (GES 300) produced by Electrical Geodesic was used. The signal recording was made in the range from 0.1 to 100 Hz, at the rate of digitization of the signal of 1000 Hz and the choice of a vertex (Cz) electrode as a translator.

Technique of "Beyley Scales of Infant Development"

To assess the cognitive sphere of infants of the control and experimental groups, crude points of the cognitive subscale of the Bayley-III scales were used. This technique is the conventional tool used for estimating development of infants aged from 1 up to 42 months [Ballot et al., 2017].

Electroencephalography technique

Registration of the EEG-data was carried out in the darkened screened room, during the procedure the research subjects were in a sitting position on a lap of the parent. For the purpose of accounting on a processing stage of EEG data of behavior of the infant and parent and also control of gaze direction of the child, process video registration, with the subsequent possibility of synchronization with an EEG curve was carried out.

During registration of EEG the quiet, monophonic, repeating video record creating a neutral visual environment, aiding to involvement of examinees in write process that allowed to lower percent of motor artifacts significantly was shown to participants of a research.

For demonstration of video the monitor (1920x1080) located at distance about 60 cm from the infant's eyes was used. As a soundtrack a quiet, melodious music was used.

At the first stage (age coverage of 5 months) of a research of infants, the Hydro Cell Geodesic Sensor Net systems with data recovery were used on oculography sensors, picked up according to the size of the head of the infant. The data traces in later life was carried out using the systems including the oculography ECG sensor located already on an infant's face. This technical feature promotes effective detection of the oculomotor artifacts and also blinking artifacts at childhood.

For primary assessment of the quality of the crude data it was carried out a visual analysis as well as the analysis of resistance value of the electrodes. Posttreatment was made with use of Net Station 5.4 EEG Software. All the EEG traces underwent the procedure of filtering using high-frequency (0.5 Hz) and low-frequency (40 Hz) filters. The EEG sections which are characterized by visual attention of the research subjects to a stimulus material; significant emotional reactions of the child and/or parent, verbal interaction and the expressed by artifact content were divided by absence into short segments lasting 2 seconds. Further automatic and manual analyses of artifacts were carried out. The assignments having poor quality of a signal were interpolated using the built-in program algorithm. Change of an EEG signal of rather general average reviewer behind which it was made by correction of the basic line became the following step of processing.

The received fragments of each research subject underwent fast Fourier transformation (FFT) with use of a Hanning window (overlapping of adjacent windows made 50%).

The power spectrum density was calculated for beta2 17-30 Hz (17.0898–30.0293 Hz) [El-Sayed, Larsson, Persson & Rydelius, 2002] and gamma 30-40 Hz (30.0903–40.0391 Hz) of [Elsabbagh et al., 2009] ranges of interest separated as a projection of prefrontal cortex divided according to the relations to left (12, 18, 19, 20, 23, 24, 27) and to the right (3, 4, 5, 10, 118, 123, 124) hemispheres [Koessler et al., 2009; Luu & Ferree, 2000].

The perimeter-wise electrodes located around the separated zone and electrodes of localization, close to them, were rejected because of a high muscular artifact content at the participants of this age group: 1, 2, 8, 9, 14, 15, 17, 21, 22, 25, 26, 32, 33, 122.

The received data of power spectrum density were subjected to normalization, with use of a formula (10*LOG10 (¼¬é/Hz)).

In the experimental group it was separated the diseased and intact hemispheres that allows to treat separately influence of affect factors on each hemisphere apart, but brings restriction in taking note of physiological lateralization of brain function for the studied indicators.

The total number of the registered the EEG traces made 158 (122 for the control group and 36 for experimental one).

The part of the traces was rejected due to the following reasons:

1. The behavior of the research subject (the moderated/expressed motion activity and/or emotional performance) during registration procedure – 46 traces (29.11%).

2. The technical reasons (failure in performance of a program algorithm, malfunction of the video data-acquisition equipment, errors of carrying out of an experimental procedure) – 3 (1.9%).

3. Emergence of discrepancy to inclusion criteria during the research period (all the data of the participant were rejected from the subsequent analysis) – 12 (7.59%).

As the result, 97 traces (61.39%) were used for the analysis.

The total number of the EEG traces for the control group included into the analysis made 70: the date of 18 infants (11 boys, 5.62 ± 0.3 months) were registered in 5 months, 21 infants (12 boys, 10.71 ± 0.55 months) in 10 months, 18 infants (8 boys, 14.51 ± 0.47 months) in 14 months, 13 infants (6 boys, 25.46 ± 0.86 months) in 24 months.

The total number of the EEG traces for the experimental group included into the analysis made 27: the date of 7 infants (6 boys, 5.44 ± 0.65 months) were registered in 5 months, 8 infants (8 boys, 11.26 ± 0.75 months) in 10 months, 7 infants (6 boys, 15.05 ± 0.44 months) in 14 months, 5 infants (4 boys, 24.82 ± 0.24 months) in 24 months.

The participants of groups were compared according to clinical and anthropometrical data at birth, for an exception of influence of a dismaturity factor (Tab. 1).

Table 1

Clinical and anthropometrical characteristics of research subjects at birth, EEG data of which were included into the analysis

Indicators	The control group; n = 55	The experimental group; n = 12
Gestional age, weeks, avg (SD)	39.5 (± 1.08)	39.57 (± 0.49)
Weight, gr, avg (SD)	3332.56 (± 462.04)	3493 (± 368.5)
Growth, cm, avg (SD)	51.55 (± 2.43)	52.7 (± 1.79)
Head circumference, cm, avg (SD)	34.09 (± 1.31)	34.36 (± 0.97)
Chest circumference, cm, avg (SD)	33.38 (± 1.66)	35.81(± 5.89)
Apgar: at 1 minutes, avg (SD)	7 (± 1)	6 (± 1)

Table 1

Clinical and anthropometrical characteristics of research subjects at birth, EEG data of which were included into the analysis

Apgar: at 5 minutes, avg (SD)	8 (± 1)	7 (± 1)
Sex, N boys (%)	29 (52.73 %)	10 (83.33 %)

Results

Statistical processing was done with the use of the *Statistical Package for the Social Sciences 23.0.*

Intergroup analysis of these Bayley-III and EEG techniques was performed by means of Mann-Whitney non-parametric U-test, due to the small sample sizes and different number of the participants in them.

A comparison of the crude points of the Bayley-III cognitive scale revealed statistically significant differences in only 5 ($p = 0.001$; $U = 12.5$) and in 24 ($p = 0.009$; $U = 5.5$) months.

The comparison of the rescaled density of power spectrum of the EEG in the prefrontal cortex projection revealed statistically significant differences of 5 months in the beta2 band ($p = 0.012$; $U = 22$) in the afflicted hemi-sphere and in beta2 ($p = 0.014$; $U = 23$) in intact hemi-sphere; 24 months: beta2 ($p = 0.013$; $U = 6$) in the afflicted hemisphere. No statistically significant differences were found in the gamma range.

Results and discussion

According to the Kennard principle on the reconstructive processes of the brain, the probability of functional recovery is higher than earlier there was a damage [Kolb, Mychasiuk, Williams & Gibb, 2011]. There is a number of the data of a clarification nature that demonstrate that actively developing brain is more sensitive to the impact of affection processes which are capable to change of its development path [Bennet et al.,2013; de Vries, 1998; Becher, Bell, Keeling, McIntosh & Wyatt, 2004].

In particular, IS which occurred in the perinatal period potentially has an elevated risk of pathological after-effects, in comparison with the cerebral thrombosis at the subsequent childhood [Ganesan et al., 2000].

The range of possible complications of IS is rather wide [Ciccone, Cappella & Borgna-Pignatti, 2011; Kirton & deVeber, 2013; Ramaswamy, Miller, Barkovich, Partridge & Ferriero, 2004; Basu, 2014; Chen et al., 2017]. The sphere of cognitive development is the most difficult in respect of forecasting of outcomes at children with this pathology. At rather similar localization of the centers of ischemia, an effect of IS can have an opposite character [Hajek et al., 2013].

Rather typically developmental children, the children with learning disability or inability to concentrate often show higher level of low-frequency power and lower levels of high-frequency power, respectively [Brito, Fifer, Myers, Elliott & Noble, 2016]. In this connection the beta2 range and the gamma range were selected as some of types of activity of the highest frequency selected in studying of the cognitive sphere [Cannon et al., 2013, Schutte, Kenemans & Schutter, 2017; Park J., Kim, Sohn, Choi & Kim, 2018, Perone & Gartstein, 2019].

The conducted research showed that the beta2 range has the greatest ratio with indicators of the cognitive Bailey-III subscale showing a deficit in 5 and in 24 months at infants with PAIS; that is why it allows to nominate it previously to a role of the effective EEG-range reflecting violations of the cognitive sphere at this pathology.

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Comparative analysis of dysfunctions in the III block of the brain in men with various types of drug addiction

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Abstract

Introduction. Drug addiction is a worldwide problem in contemporary society. The lack of neuropsychological information on the characteristic features of higher mental functions in men with various types of drug addiction, as well as the social significance of the problem represent unmet needs necessitating a comprehensive solution. The article provides findings of a comparative study of the functional state of the third block of the brain in healthy drug-dependent men.

Methods. The study used methods of neuropsychological diagnostic assessment of A. R. Luria (modified by T. V. Akhutina), and of statistical analysis (descriptive statistics, one-way analysis of variance SPSS for Windows).

Results. The programming and control functions, the function of the serial organization of movements and speech were studied, statistically significant differences between healthy and sick men were determined. No significant differences were found between groups of drug users depending on the specific drug.

Discussion. The findings of the study demonstrate the impairing effects of opioids and cannabinoids on the functions of the third block. The changes were mostly related to the ability to master a program and to automate motor skills, to act complying with voice instructions and to switch over according to their modifications. No significant differences in revealed disorders were observed between subjects with different types of drug addiction. However, an analysis of the individual characteristics of the task performance showed that opioid addicts, as well as addicts with the combined use of different drugs, more often made mistakes when performing experimental tasks compared to cannabinoid-addicted patients. Moreover, mistakes made by the subjects of the former groups were rougher and more repetitive. There is evidence in the available literature consistent with our findings and contradicting them. Further research is needed to clarify these issues.

Keywords

neuropsychological analysis, mental functions, brain block, drug addiction, opioids, cannabinoids, addiction

Highlights

► drugs (opioids and cannabinoids) clearly impair functions of the third block of the brain;

► abilities to master a program and to automate motor skills are most impaired;

► the destructive effect of drugs affects the ability to act according to voice instructions, switch over according to their modifications.

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Introduction

It is well known that drugs impact various systems and structures of the brain, resulting directly in a pathological addiction (Anokhina, Klimenko, Gabril'yants, & L'vova, 2018; Ivanets, Pylaeva, & Shatenshtein, 2011; Agibalova & Poplevchenkov, 2012; Antsyborov & Morykhin, 2017; Ilyuk et al., 2017; Klimenko, Kozlova, Istomina & Bespalova, 2013; Litvintsev, 2015; Poplevchenkov & Agibalova, 2017; Skryl', 2013; Chernobrovkina, 2015; Chizhova, Mishkina, Pilyavskaya et al., 2013; Chukhrova, 2013; Aguado et al., 2007; Kalwa & Habrat, 2015; Castaneto et al., 2014; Murray, Farrington & Sekol, 2012). The toxic admixtures in drugs increase the destructive effect of the main substance on the central nervous system.

In the available literature, there are studies on the neuropsychological characteristic features of drug addicts. Among the well-described disorders of mental functions in drug addicts syndromes related to the damage anterior parts of the brain (III block) are of special interest. It is assumed that a decrease or an impairment of regulatory functions is an imminent characteristic of any addiction (Shuvalova, & Tsvetkov, 2016).

The consumption of cannabis leads to impairment of the ability to combine and compare information, lack of desire to interpret opinions and motives of others, emotional emptiness (Lundqvist, 2005). The “inner activity plans” are blown, social motives decreased, interest on the long-term planning, programming behavior disappears. Self-criticism and activity control reduce.

Heroin addiction is associated with disorders of the functions of mediobasal sections of the frontal region as well as of diencephalic limbic structures and the dysfunction of convexital areas of the frontal cortex (Baulina, 2002). Persistent impairment of neuropsychological factors settled in the convexital prefrontal cortex does not depend on the stage of the withdrawal syndrome or on the effects of treatment medicaments (Kovshova & Prosvetova, 2015).

Simultaneous or successive use of different psychoactive substances increases the risk of negative effects on the body (Yaltonskii, Sirota, & Yaltonskaya, 2017). Patients with a combined addiction to heroin and alcohol are characterized with more pronounced impairment of visual memory and learning ability, lower reactions switching and cognitive flexibility levels, less problem-solving efficiency compared to patients with isolate heroin addiction (Bushara et al., 2009). A mild, but long-term decrease in executive characteristics of intelligence and memory is characteristic for individuals who use "ecstasy" to cope with cannabis withdrawal symptoms (Klugman & Gruzelier, 2003).

Available neuropsychological findings are of interest to be investigated further.

It is known that the III functional block of the brain ensures the organization of the dynamic, conscious, purposeful activity and is associated with the management of functions of serial movements or speech (A. R. Luria).

Our pilot study enrolled 108 men (4 groups) of middle age (age categories by D. Bromley) registered in the drug abuse clinic. The first group included opioid-addictes patients (according to ICD-10, code F11.2), the second group included patients addicted to cannabinoids (F12.2), the third group comprised patients combining opioids with cannabinoids (F19.2).

The fourth group comprised men without drug addiction disorders. Patients with epilepsy, schizophrenia, severe neurological symptoms, severe somatic pathology, and history of craniocerebral trauma were excluded from the study.

Methods

To characterize the functioning of the third block of the brain in men with various types of drug addiction, neuropsychological diagnostic methods developed by A. R. Luria and modified by T. V. Akhutina were used. To study characteristic features of programming and control functions, we used tests for the choice behavior, rhythmic drawing according to instructions, retelling a text and performing oddball tasks. To study the functions of serial organization of movements and speech, we used tests for dynamic praxis, reciprocal and graphomotor coordination, retelling a text (grammatical arrangement criterion). Data were statistically processed with descriptive statistics methods and one-way analysis of variance (based on the SPSS for Windows software package).

Results

The study of the programming and control functions revealed significant differences between healthy and sick men (see Table 1). The results of the oddball test showed significantly higher maturity levels for verbal-logical operations of classification and generalization in healthy subjects compared to the drug-addicted men ($p < 0.000$). Among the drug-addicted, no significant differences between groups were identified. However, it was noted that patients addicted to cannabinoid coped with tasks more successfully compared to the subjects from groups 1, 3. Data of the test for the choice behavior suggest that healthy men ($p < 0.000$) have a better ability to act according to voice instructions, to regulate their actions suppressing immediate reactions contradicting instructions.

Table 1

Programming and control function differences (scores)

Parameters of the function	ANOVA		1*	2	3	4
	F	p	Mean	Mean	Mean	Mean
Accuracy in an outside term elimination	6.32	0.001	2.9	3.1	2.9	3.9
Accuracy in an outside term explanation	10.6	0.000	2.5	2.8	2.2	3.8
Productivity in the choice behavior test	10.4	0.000	2.69	2.39	2.5	3.82
Assimilation when performing the choice behavior test	5.05	0.001	0.5	0.5	0.6	0.12
Text retelling (logical adequacy)	15.8	0.000	1.4	1.7	1.1	2.6
Text retelling (composition ability)	17.4	0.000	1.29	1.5	1.2	2.48

Notes: 1 –opioid-addicted group, 2 –cannabinoid-addicted group, 3 – combined opioid and cannabinoid using group; 4 – healthy controls*

The study of the ability to the serial organization of movements and speech in healthy men and men with various types of addiction has shown that the use of psychoactive substances noticeably impairs it.

Table 2

Differences in the function of the serial organization of movement and speech (scores)

	ANOVA		1	2	3	4
Parameters of the serial organization	F	p	Mean	Mean	Mean	Mean
Dynamic praxis (mastering skills)	3.7	0.13	2.81	2.86	2.47	3.38
Dynamic praxis (automating skills)	31.5	0.000	1.78	1.79	1.47	3.65
Dynamic praxis (serial organization)	12	0.000	2.1	2.2	1.93	3.47
Dynamic praxis (clumsiness)	19.1	0.000	0.19	0.14	0.27	0.00
Reciprocal organization (productivity)	21.2	0.000	2.59	2.25	1.33	3.85

Table 2

Differences in the function of the serial organization of movement and speech (scores)

	ANOVA		1	2	3	4
Parameters of the serial organization	F	p	Mean	Mean	Mean	Mean
Reciprocal organization (interhemispheric interplay)	2.13	0.000	0.66	0.68	0.93	0.06
Graphomotor coordination (serial expression)	8.32	0.000	2.44	2.5	2.13	3.85
Text retelling (grammatical arrangement)	18.62	0.000	1.75	1.92	2.06	2.78

Healthy individuals master a movement series with the leading hand when performing the dynamic praxis test more successfully (see Table 2) ($p < 0.000$). The average rates of the ability to automate motor skills are significantly higher in healthy men compared to addicted ($p < 0.000$). The addicted patients performed series of movements with the leading hand significantly worse ($p < 0.000$) and more often demonstrated clumsiness when performing the test ($p < 0.000$).

A qualitative measurement of test performance showed the characteristic fluency of healthy control subjects when performing the motor program (see Fig. 1) (70%). Whereas drug addicts more often performed the test for dynamic praxis "in bursts". It should be noted that cannabinoid-addicted subjects (32%) were more able to switch from delayed or "in bursts" performance to correct fluent movements compared to the opioid-addicted (18%) or to the combined opioid-cannabinoid-addicted (14%). Opioid-addicted subjects (15%) more often than other addicted (7% in the group 2, 2% in the group 3) in this sample made bad mistakes (failures when increasing the pace or element-by-element performance).

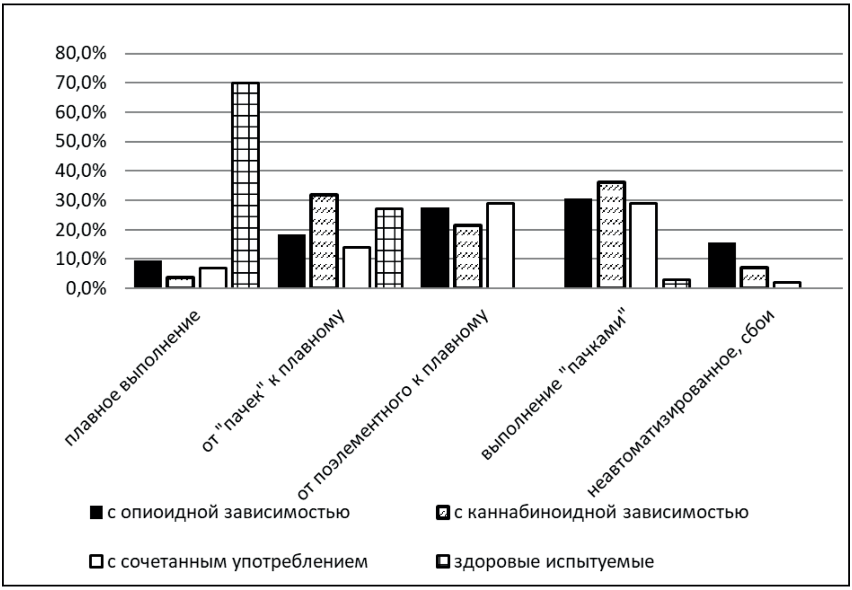

Figure 1. Distribution of subjects depending on the successfulness of the dynamic praxis performance

Noteworthy, differences in the reciprocal coordination scores between the groups were significant ($p < 0.000$). The productivity of the task performance was higher in healthy subjects compared to addicted patients (see Table 2). This indicates not only the difficulties in the serial organization of movements in the drug-addicts but also a decrease in the possibility of the interhemispheric interaction.

Significant differences in parameters of the graphomotor coordination the performance between healthy and drug-addicted individuals suggest that there is a significant decrease in the serial organization function in subjects with opioid ($p < 0.001$), cannabinoid ($p < 0.008$) or combined ($p < 0.002$) addictions (see Table 2). Healthy people had a higher rate of performance accuracy (26%) and made fewer mistakes (see Fig. 2). Opioid-addicted individuals often made mistakes of the "site" type (49%) along with mistaken assimilation of elements and replacing vertical lines with gently sloping ones (30%). Cannabinoids consumers most often stopped in the course of the test (23%). Individuals with combined drug addiction made the worst mistakes in their drawings: mistakes with the program expansion (20%).

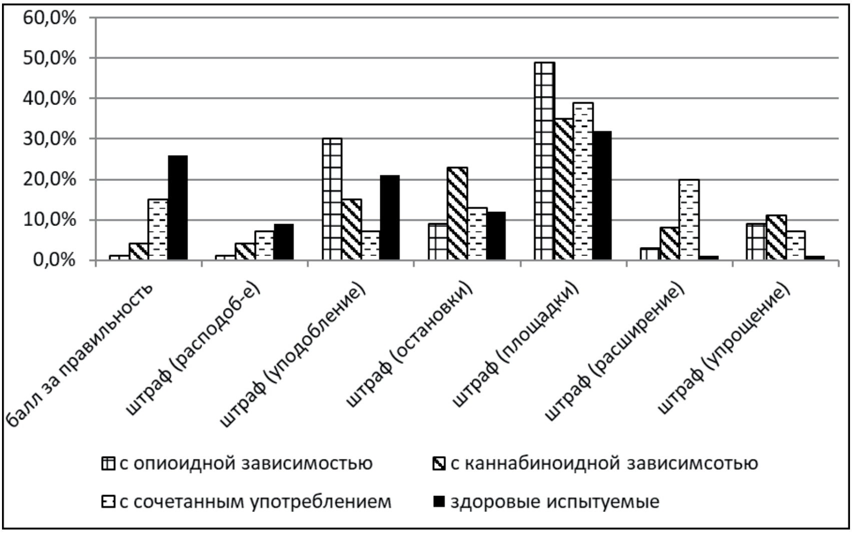

Figure 2. Characteristics of the serial organization in the graphomotor coordination test

Healthy subjects (see Table 2) had higher rates for the grammatical arrangement of the text ($p < 0.001$), using easily more complex and diverse grammatical constructions and detailed retelling.

Discussion

The functions of the III block of the brain suffer changes when they are influenced by opioids or cannabinoids. The serial organization of movements and speech clearly deteriorates, most of all the ability to master the program and automate motor skills. In addition, the destructive effects of drugs manifest themself in the ability to act complying with speech instructions, switching according to its modifications. These findings are consistent with the results of studies of other authors investigating the neuropsychological aspects of drug addiction (Shuvalova & Tsvetkov, 2016; Kovshova & Prosvetova, 2015; Baulina, 2002; Klugman & Gruzelier, 2003; etc.). In the literature, there are also other opinions. Thus, Van Holst & Schilt (2011) argue that a persistent deficit in executive regulatory functions is associated with the use of all narcotic substances but cannabis. It is important to note that the authors in their review focused on studies with small samples, were control groups included former marijuana users within the two-week abstinence period. An opinion exists that the chronic effects of the isolated use of cannabis on brain activity may be unstable, so more sensitive methods are needed to evaluate them. Klugman & Gruzelier (2003) noted a pronounced attention-deficit under the influence of cannabis, discovered in electrophysiological studies. Thus, the use of different-type methods to identify impairments, small sizes of samples as well as methodological inaccuracies may be responsible for the inconsistency of reported empirical data (Perfilova, 2019; Fotekova & Kicheeva, 2012).

In our study, no significant differences were found between different groups of drug users. However, an analysis of individual performance characteristics (see Fig. 1, 2) showed that opioid-addicted individuals, as well as combined drug addicts, more often made mistakes when performing experimental tasks compared to cannabinoid-addicted patients, and moreover, they made rougher and more repetitive mistakes. This echoes the opinion of Yaltonskii et al. (2017). Researchers note that the combined use of different drugs and other psychoactive substances is associated with higher neurotoxicity and leads to neurodegenerative changes and neurocognitive deficiency.

Further researches are needed to clarify these issues.

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Electroencephalographic correlates of the activity of the frontoparietal system as predictors of verbal intelligence and non-verbal creativity

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Abstract

Introduction. It is known that the frontoparietal system is involved in both intellectual and creative functions, but no consensus has been achieved on the issue of how these functions and the associated activity of the frontoparietal parts of the brain interplay and reflect each other. The purpose of this study was to identify patterns of neuronal oscillations, which could be predictors of verbal or figurative components of intelligence and/or imaginative creativity.

Methods. The activity of the frontoparietal cortex was analyzed using multichannel electroencephalography (EEG) technique. The study enrolled 37 university students. The EEG baseline power values of 6 frequency bands, from delta to beta2 were analyzed in comparison with the verbal (IQv) and figurative (IQf) components of intelligence assessed using the Amthauer technique and with the imaginative originality when performing the Torrance subtest "Incomplete figures task" (IFT).

Results. When comparing groups with high or low IQv or IFT rates, the following general effects were established: asymmetry in the activity of anterior and posterior-frontal regions in the beta1 frequency band and higher power values of the delta rhythm in frontal regions of the cortex in individuals with higher IQv rate, and in the central-parietal cortex in individuals with higher imaginative originality rates, respectively, along with higher values of the alpha1 rhythm in the central and the alpha2 rhythm in the frontal areas of the cortex. Regression models calculated for IFT and IQv were similar, delta rhythm power values in the frontal leads of the left hemisphere being the main predictor of intellectual and creative abilities.

Discussion. The similarity of the regression models for IFT and IQv with more pronounced differences in frequency and regional representation of the EEG correlates of the imaginative originality should be considered as evidence that intelligence (and the structures associated with it) is a necessary but not sufficient condition for creativity. The detected frequency-spatial relationship between the IFT and IQv may arise from the similar organization of executive control over the imaginative task performance.

Keywords
frontoparietal system, electroencephalography, delta oscillations, alpha oscillations, beta oscillations, verbal intelligence, non-verbal creativity, imaginative originality

Highlights

► The background activity of the frontal areas of the cortex in the low-frequency delta and high-frequency beta bands is a predictor of both non-verbal creativity and verbal intelligence.

► With the general similarity of the regression models of non-verbal creativity and verbal intelligence, in individuals with higher imaginative originality rates additional changes in the power of alpha1, alpha2, and beta2 oscillations have been revealed.

► The background activity of the frontoparietal system associated with imaginative originality is represented more broadly both in the frequency range and brain regions in comparison with EEG correlates of verbal intelligence.

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Introduction

Recent intensive studies neurophysiological correlates of creativity revealed the key importance of the frontoparietal system functions associated with the search for new ideas or executive control when choosing an original solution to the problem (Beaty, Benedek, Wilkins, & Jauk, 2014; Beaty, Seli, & Schacter, 2019; Gulbinaite, van Rijn, & Cohen, 2014; Heinonen, Numminen, Hlushchuk, Antell, Taatila, & Suomala, 2016). On the other hand, the interaction of these brain regions is considered as the neurophysiological basis for the implementation of one's intellectual abilities (Beaty et al., 2014; Jung & Haier, 2007; Hearne, Mattingley, & Cocchi, 2016; Lee et al., 2006; Pamplona, Neto, Rosset, Rogers, & Salmon, 2015), which is not surprising, given the need for executive control of problem-solving during intelligence testing. However, using the recent technique of diffusion tensor imaging and tractography a specialization in the interaction of the structures of the frontoparietal system and the brain default mode network (DMN) associated with intelligence or creativity was revealed. Intelligence was shown to be represented by a system for “easy” achievement a functional state with activation of the right upper parietal region, while the left retrosplenial cortex has low integration abilities; creativity at that, as evaluated with verbal subtests of Torrens, turned out to be represented by a system of "elaborate" switching of connectivity of cortical regions with a center in the right dorsolateral prefrontal cortex with high integration abilities of the sensorimotor cortex (Kenett, 2018). Moreover, the integral indicator of the originality of responses was characterized by a connectivity "hub" region in the posterior part of the superior temporal gyrus, suggesting that speech functions were involved in the generation of ideas. Analysis of the brain activity related to non-verbal creativity, along with a widespread bilateral neuronal network, demonstrated the dominance of the left hemisphere, including the left dorsolateral prefrontal cortex (Aziz-Zadeh, Liew, & Dandekar, 2013) or the left anterior singular cortex (Hahm, Kim, Park, & Lee, 2017), which are considered to be necessary to find an original solution to a problem.

Traditional methods of EEG analysis continue to be widely used to investigate mechanisms of the functional interaction of cortical areas, along with modern functional magnetic resonance imaging technique (fMRI) (Herrmann, Strüber, Helfrich, & Engel, 2016; Stevens & Zabelina, 2019). As an indicator of activation or inhibition processes in neuronal networks among frequency bands of biopotentials alpha rhythm is often preferred (Benedek, Jauk, Sommer, Arendasy, & Neubauer, 2014; Fink & Benedek, 2014; Lustenberger, Boyle, Foulser, Mellin, & Fröhlich, 2015; Razumnikova, 2007). Creativity-related changes in the synchronization of alpha biopotentials in the frontal areas noted by different authors turn out to be dependent on both the level of intelligence and creativity of experiments subjects (Benedek et al., 2014; Lustenberger et al., 2015; Razumnikova, 2009a; Dikaya & Dikii, 2015; Nagornova, 2007; Benedek, Bergner, Könen, Fink, & Neubauer, 2011). The positive relationship between intelligence and creativity have been confirmed by the results of both psychometric and neurophysiological studies (Jauk, Benedek, Dunst, & Neubauer, 2013; Karwowski et al., 2016; Nusbaum & Silvia, 2011; Preckel, Holling, & Wiese, 2006). However, there is no consensus about the "threshold" effect in the ratio of these psychometric constructs (Jauk et al., 2013; Nusbaum & Silvia, 2011; Preckel et al., 2006) or on regional specificity of this effect (Benedek et al., 2014; Razumnikova, 2009b; Arden, Chavez, Grazioplene, & Jung, 2010; Jung, Mead, Carrasco, & Flores, 2013; Pidgeon et al., 2016). This study based on structural approach with latent variables investigated roles of three specific components of the executive system: information resources updating, switching, and inhibition, as well as their general and differential relations with fluid intelligence and divergent thinking abilities. It turned out that inhibition and updating of working memory are predictors of creativity; the latter component also determines the variability of IQ (Benedek et al., 2014). The balance between the background activity of the frontal and posterior cortex is considered as a basis of choosing an individual cognitive style, including the preferences for an insight or an analytical strategy for solving problems (Benedek et al., 2014; Erickson et al., 2018; Kounios et al., 2008). Predictors of this balance are low-frequency theta, alpha, and high-frequency beta oscillations (Heinonen et al., 2016; Stevens & Zabelina, 2019; Solomon et al., 2017).

Earlier, in another study using a heuristic problem as a model of creativity it was shown that individuals with high intelligence and creativity rates are characterized with enhanced interaction of neuronal ensembles in the anterior cortex and left hemisphere in contrast with those with lower rates of these parameters (Razumnikova, 2009a). This conclusion was drawn based on the analysis of EEG coherence, and the effects of the interaction of the factors "creativity" and "intelligence" were presented in a wide range of frequency bands from theta1 to beta 2, for the imaginative intelligence parameters, predominantly.

According to the classical conception of the two- stage creative thinking, the generation of ideas is associated with diffuse attention and bottom-up neuronal processes, and their evaluation with focused attention and executive control, i.e. top-down processes (Jung et al., 2013). These processes are ensured by the cooperation of the DMN and the executive control system (Beaty et al., 2014; Benedek et al., 2014). Since the state of the DMN reflects a variety of individual personality characteristics, including intelligence or creativity (Beaty et al., 2019; Li, Yang, Zhang, Li, & Qiuc, 2016; Takeshi, Aihara, Shimokawa, & Yamashita, 2018), it is not surprising that the unique interaction of these neuronal structures creates variable patterns of the activation-inhibition processes, which are reflected in the frequency-spatial EEG characteristics. In this regard, the purpose of the study was to elucidate such patterns of neuronal oscillations in the frontal and central areas of the parietal parts of the brain which are associated with verbal or visual-spatial components of intelligence and creativity and could serve as their level predictors.

Research hypotheses:

– background activity of the frontoparietal system of the brain is associated with psychometric indicators of intelligence and creativity with a broader frequency-spatial representation for imaginative originality;

– models for describing intelligence and creativity have similar EEG predictors of the activity of the frontal cortex, and regionally and frequency-specific predictors.

Methods

The study involved 37 people (students 18 ± 1.1 years old; 27 females and 10 males).

To determine the verbal and imaginative (visual-spatial) components of intelligence, we used the Amthauer intelligence structure test. Imaginative creativity was assessed using the Torrens subtest "Incomplete figures task". The originality index was calculated with a computerized technique as a number inverse to the number of drawings with identical ideas to those stored in the database (Razumnikova, 2002).

EEGs were recorded in subjects in a state of quiet *wakefulness* with eyes closed using Mitsar-201 hardware and software in the 19 leads (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4 , T5, P3, Pz, P4, T6, O1, O2), arranged according to the 10/20 system, with an integrated reference ear electrode. To analyze the brain activity, 2-second artifact-free EEG segments were selected with a total duration of 60 sec. The EEG spectral density was calculated in each lead in six frequency bands: delta (1–4 Hz), theta (4–7 Hz), alpha1 (7–10 Hz), alpha2 (10–13 Hz), beta1 (13–20 Hz) and beta2 (20–30 Hz), using the fast Fourier transform technique. For statistical analysis, the natural logarithm of the EEG power values was used.

Results

The intelligence and originality rates when performing figurative creativity tasks in the groups of males and females did not differ significantly ($0.40 < p < 0.65$), and further analysis was performed for the whole series of subjects. Correlation analysis revealed positive relationship between IQv and IQs rates ($r = 0.39$, $P < 0.015$). Significant correlations with the rates of the imaginative originality were not found for IQv nor IQs ($r = 0.25$ and 0.06, respectively).

To further analyze the EEG correlates of IQv, IQs, and creativity, subjects were classified into groups with high (IQv1, IQs1, IFT1) or low (IQv0.IQs0.IFT0) ratings of intelligence and imaginative originality, based on the average rates for each parameter. Characteristics of the groups and the rates of intelligence and creativity are summarized in Table 1 (there was a significant intergroup difference: $6.78 < t < 9.33$, $P < 0.00001$).

Table 1

Characteristics of groups with high or low rates of intelligence or creativity for comparative analysis

Parameter	High rates		Low rates	
	n	values	n	values
Verbal IQ	20	109,2 ± 3,3	17	100,0 ± 5,0
Visual and spatial IQ	17	112,4 ± 4,6	20	100,9 ± 3,7
Originality of imaginative creativity	14	2,6 ± 0,6	23	4,9 ± 0,8

According to the purpose of the study the activity characteristics in the frontal and central parietal (CPariet) cortical regions for each frequency band were analyzed with one-way ANOVA test for every pairs of independent factors: IQv1/IQv0, IQf1/IQf0 or IFT1/IFT0. The effects revealed in the IQv or IFT analyses are summarized in Table. 2. For IQf no significant effects were detected.

Table 2

Results of the analysis of variance between groups with high or low rates of intelligence or creativity parameters

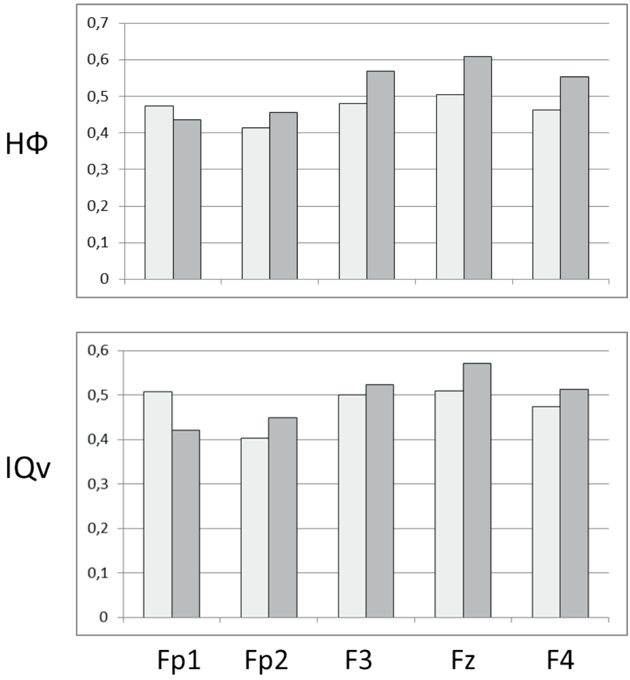
Parameter	Frequency	Area	F	df	P	Effects
IQv	Delta	Front	4,67	1.35	0,04	IQv1 > IQv0
IFT			3.53		0.07	IFT1 > IFT0
		CPariet	3.91		0.05	
IFT	Alfa1	CPariet	2.62	5.175	0.03	IFT1 > IFT0 in C3, Cz, C4
	Alf 2	Front	2.15	6.210	0.05	IFT1 > IFT0 in Fz, F4, F8
IQv	Beta1	Front	2.62	6.210	0.02	IQv0 > IQv1in Fp1, but IQv1 > IQv0 in Fp2, F3, Fz, F4
IFT			2.78		0.01	Fp1: IFT0 > IFT1, Fp2, F3, Fz, F4: IFT1 > IFT0
IFT	Beta2	Front	2.50	6.210	0.03	Fp1: IFT0 > IFT1, Fz, F4: IFT1 > IFT0

Notes: Front, frontal cortical areas, CPariet, *central parietal cortical areas*

Within the delta frequency band a general effect for IQv was revealed: in the frontal cortex the power of these low-frequency oscillations was higher in the IQv1 group than in the IQv0 group. A similar effect was noted for the frontal areas as a non significant trend, and for the central parietal areas as a significant difference between groups with different levels of imaginative originality. Within the alpha frequency band the higher EEG power values differed depending on regions: the power values for the alpha1 band they were significantly higher for the IFT1 vs the IFT0 group in central regions of the cortex, and for the alpha2 band they were higher in the frontal regions with dominance of the right hemisphere (Fz, F4, F8).

Within the beta1 frequency band EEG power values were lower in the high IQv and high imaginative originality groups as compared to the IQv0 and IFT0 groups in the left anterior-frontal lead with inversion of this effect for all other areas of the prefrontal cortex (Fig. 1). The same asymmetry effects for beta2 oscillations in the frontal cortex were also revealed between the IFT groups, but not between the IQv groups (see Table 2).

Thus, ANOVA results revealed the similarity of the activation effects in the frontal cortex delta and beta1 bands associated with verbal intelligence and imaginative originality levels. At the same time, it should be noted that the EEG changes associated with creativity as opposed to those associated with IQv are presented more broadly both for regions involved (posterior cortex), and for frequency bands (alpha1.2 and beta2 oscillations).



(НФ = IFT)

Figure 1. Regional characteristics of the beta1 rhythm power values in the frontal leads depending on the level of the imaginative originality (IFT) or verbal intelligence (IQv)

The functional role of the detected intergroup differences in the background EEG power values has been analyzed using the regression analysis: imaginative originality or verbal intelligence were considered as independent variables, the power values for frequency bands and leads identified at the previous analysis stage were chosen as dependent variables. Linear regression with stepwise addition of dependent variables was used.

The correlation analysis of EEG indicators confirmed the absence of multicollinearity. The opposite correlations in different groups were found for the delta and beta1,2 rhythms power in the anterior frontal leads: positive in the IFT0 group and negative in the IFT1 group ($0.07 < P < 0.04$). With no vital differences in the delta and beta1 rhythms between the IFT0 and IFT1 groups in other cortical areas the average delta or beta2 rhythms power values in the frontal cortex were more stable for the IFT1 group compared to the IFT0 group ($r = 0.63$, $p < 0.02$ and $r = 0.36$, $p < 0.1$, respectively). This effect of a better coherence between the delta and beta2 rhythms in the IFT1 group was observed in the leads F3, F7, F4, Cz, C3 ($0.52 < r < 0.61$, $0.02 < p < 0.05$).

As for the IQv groups, correlation analysis of the average rhythm power values revealed a significant association between delta and beta2 rhythms in the back cortex for the IQv1 group without regional lead-depending specificity of this effect. For the beta1 band rhythms positive correlation of rhythms in the IQv0 group was observed generalized throughout all leads except the anterofrontal ones; in the IQv1 group, the correlations of delta and beta1 oscillations were significant only in the parietal regions in the leads F3, F4, F8.

The best models for IFT or IQv obtained in the regression analysis of the delta and beta rhythms are shown in Table 3. The correlation coefficient between the selected dependent variables, power values of the delta and beta1 or beta2 rhythm, turned out to be lower than 0.27, which rules out the effect of multicollinearity of the dependent variables. Contribution of the power values of alpha 1.2 oscillations did not improve the descriptive possibilities of the regression models for IFT.

According to the regression models, about 5% of the IFT dispersion can be predicted either by the average power values of the delta rhythm in the frontal areas of the cortex, or values in the leads F3 or F4. Beta1 or beta2 rhythm values in the anterofrontal lead of the left hemisphere added to the regression model increased its descriptive possibilities (R^2 increased up to 16–17 %), however, contribution of the of high-frequency oscillations power values was not significant (see Table 3).

The regression models for IQv turned out to be similar to those obtained for IFTs, with the only exception that the F7 lead values substituting for the F3 ones: the delta rhythm power in the F7 lead predicts about 16% of IQv variability. The introduction of beta power values into the regression analysis increased the R^2 up to 21–23%, however, just as in the models for IFTs, these high-frequency IQv predictors are not significant ($0.08 < p < 0.16$).

Table 3

Main parameters for regression models for the originality (IFT) and the verbal intellect (IQv) rates

Frequency bands	Area	F	df	p_F	R^2	β	t	p_t
IFT								
Delta	Front	4.04	1.35	0.05	0.10	0.32	2.01	0.05
	F3	4.29		0.05	0.11	0.33	2.07	0.05
	F4	4.11		0.05	0.10	0.32	2.03	0.05
Delta	F3	3.57	2.34	0.04	0.17	0.41	2.50	0.02
Beta1	Fp1					–0.26	–1.62	0.11
Delta	F3	3.24		0.05	0.16	0.36	2.29	0.03
Beta2	Fp1					–0.23	–1.44	0.16
IQv								
Delta	Front	3.39	1.35	0.07	0.09	0.30	1.84	0.07
	F7	6.58		0.01	0.16	0.40	2.56	0.01
	Fp1	3.02		0.08	0.09	0.28	1.74	0.08
	Fp2	3.25		0.08	0.09	0.29	1.80	0.08
Delta	F7	4.41	2.34	0.02	0.21	0.43	2.78	0.01
Beta1	Fp1					–0.22	–1.43	0.16
Delta	F7	5.14		0.01	0.23	0.41	2.70	0.01
Beta2	Fp1					–0.27	–1.80	0.08

Discussion

Findings obtained by the intergroup comparison are consistent with the idea of the intelligence (and the structures associated with it) as a necessary but not sufficient condition for creativity (Karwowski et al., 2016). Moreover, the necessary condition for imaginative creativity turned out to be the verbal intelligence, because of the involvement of speech functions both in the ideas generation (Kenett et al., 2018) and in the organization of executive control when performing a task. These two components of creativity might be associated with different oscillatory components of the background activity of the cortex: executive control relating to the delta activity (Knyazev, 2007, 2012), and speech functions relating to the beta1 activity (Pulvermuller, Birbaumer, Lutzenverger, &

Mohr, 1997). An increase in the power of biopotentials detected in the alpha1,2 frequency band in subjects with high imaginative originality supports the concept of "pre-setting" of the background state of the brain (Kounios et al., 2008), facilitating realization of internal attention and inhibition processes in divergent thinking (Benedek et al., 2011).

The more pronounced representation of the synchronization effect for delta oscillations in the IFT1 compared to the IFT0 group, where it covers not only the frontal, but also the central parietal parts of the cortex, reflects the potential possibility to connect to the distributed neuronal network of the multimodal information as a resource for the creative activity. Indeed, using fMRI, the interaction of the frontoparietal system and DMN has been shown to be integral to generate conceptually new solutions when performing tasks testing imaginative creativity (Christensen, Benedek, Silvia, & Beaty, 2019). The effective coordination of neuronal ensembles of this distributed system requires synchronization of the slow wave activity, according to our data and the results of an earlier study, where, in addition, a positive relationship between delta oscillations and originality of divergent thinking were observed (Boot, Baas, Mühlfeld, de Dreu, & van Gaal, 2017).

The similarity of the obtained models for ITF and IQv can be considered as a potential ability to use different strategies, both insight and analytical ones when performing an imaginative creative task, moreover, the ability to differentiate these cognitive strategies is supported with beta oscillations in the background EEG (Erickson et al., 2018), the power of which is an additional predictor of dispersion both for IFT, and IQv, according to the regression models.

A steady contribution to the regression models of both IFT and IQv made by the delta biopotentials in the left frontal cortical regions may reflect the ability to control the cognitive activity additionally with motivational potential (Knyazev, 2007) and to coordinate the activity of spatially distributed neuronal networks to search for an original solution, as it was noted earlier (Bhattacharya & Petsche, 2005). However, there exists evidence of an opposite reaction as well: generation of a unique image can be associated with a lower level of delta oscillations (Foster, Williamson, & Harrison, 2005). Perhaps such contradictions reflect the effect of a subjective overestimation of the task complexity which affects the balance of activation and inhibitory processes in the cortex (Razumnikova, 2009a). The regional specificity of the predictors for IFT or IQv (leads Fp1, F3, F7) is consistent with the planning functions of the left part of the dorsolateral prefrontal cortex, which part performs a targeted search for a solution to a problem (Aziz-Zadeh et al., 2013). The connectivity factor of the left part of the frontoparietal system and the anterior part of the DMN correlates positively with the originality of solutions to divergent problems (Shi et al., 2018).

An additional contribution of the beta rhythm to the model can be interpreted as part of the control of image reproduction using the associative-semantic network when performing creativity tasks. Moreover, the negative sign of the beta1,2 rhythms power values in the left anterior-frontal cortex (Fp1 lead) may be the evidence of a negative role of the accelerated image reproduction in the task with completing figures, since presented stimuli primarily bring to mind the most common stereotypical objects. This hypothesis is supported by findings on the functional importance of the left prefrontal areas for the fluent generation of ideas (Hirshorn & Thompson-Schill, 2006).

Conclusion

An analysis of the background activity of the frontal and central-parietal cortical regions in six frequency bands from delta to beta2 revealed, that only the delta and beta1 oscillations power values are predictors of both non-verbal creativity and verbal intelligence. With similar regression models of imaginative originality and the verbal component of intelligence, stratification of individuals by imaginative creativity levels reveals associated differences in power values of the alpha1, alpha2, and beta2 frequency bands, which are represented not only in the frontal but also in the central parietal cortex. Identified EEG correlates of verbal intelligence and imaginative creativity suggest that the relationship between intelligence and creativity is mediated by the frontal system of executive control of the cognitive activity.

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The Dynamics of Brain Activity During Adaptation to Restrictions of External Performance of an Element of Individual Experience

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Abstract

Introduction. This study concentrates on changes in individual experience when the external performance of one of its elements – namely, the system that is formed during learning this behavioral act – becomes impossible. The circumstances entailing inability to perform the behavior that have previously helped to achieve results are considered as ‘restriction’. The primary objective of this study was to identify possible modifications in the structure of individual experience when one of its elements cannot be performed, which is reflected in changes in the characteristics of neural activity.

Methods. Neuronal activity in rat cortex was recorded during restricted food-seeking instrumental behaviors, when we removed the pedal in one side of the cage, which was previously associated with feeding. In order to determine the patterns of neuronal activity and to analyze its dynamics we recorded it before restriction of definitive behavior, and after restriction in the opposite side of the cage when the pedal was not removed.

Results. Compared to definitive behavior, changes in neuronal activity in terms of restriction are mainly associated with the loss of the ability to perform behaviors leading to goal achievement. The results speak in favor of neurons that were activated in preserved behavior and changed their activity in terms of restriction (which was possible both before and during restriction).

Discussion. The findings confirm modifications in the structure of individual experience associated with restrictions of external performance of one of its elements that affect not only the restricted element of experience, but also the elements associated with it. Experiments aimed at identifying mechanisms influencing memory in animals are important for understanding the dynamics of human memory, as well as for developing approaches to its ‘editing’ in clinical practice.

Keywords
individual experience, neuron activity, behavior, restrictions of performance, adaptation, inconsistency, learning, reconsolidation modification, element of experience, instrumental extinction

Highlights

► Restrictions of ‘external’ performance of an element of individual experience involves modifications in its structure, which is accompanied with changes in the dynamics of brain activity.

► Changes in the structure of individual experience affect not only an element of experience, which ‘external’ performing is directly subjected to restriction, but also other related elements.

► Events entailing the impossibility of ‘external’ performance of an element of experience change the characteristics of animal behavior.

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Introduction

The present study attempts to investigate the changes in individual experience when the ‘external’ performance of one of its elements becomes impossible. In contrast to the ‘internal’ performance of an element, the ‘external’ one means the implementation of this act in the external environment, which leads to the achievement of the result of this act. A system-evolutionary approach in psychophysiology underlay the methodology of this study (Shvyrkov, 1995; Aleksandrov, et al., 1997). Within the system-evolutionary approach, the concept of ‘individual experience’ – the main subject of psychology – is applied to a structure which can be empirically studied using certain methodological techniques (Ponomarev, 1983; Aleksandrov, 2006). The concept of ‘individual experience’ describes a psychological structure representing an assembly of models of individuals’ interaction with the environment and providing a fixation and reproduction of certain interactions.

The elements that constitute individual experience are functional systems (Anokhin, 1975). In each new episode of learning individuals acquire a new element of experience that joins the already existing structure. The functional system of a behavioral act (an element of experience) is associated with a certain group of specialized neurons (Shvyrkov, 1995). The specialization of neurons is expressed in their absolute activation when individuals perform certain behavioral acts. The systemic specialization of the neuron is largely determined by the genetic program and is constant (Shvyrkov, 1995; Aleksandrov, 2005).

Thus, the formation of a new element of experience is associated with the acquisition of systemic specialization by a group of neurons. The acquisition of new neural specializations starts with a situation of inconsistency, when the available result does not satisfy the needs of the organism and the existing behavior models fail to solve actual problems (Aleksandrov, 2005). Novel events contribute to significant increases in expressions of early genes (the c-fos gene, in particular), representing an initial stage of the cascade of molecular biological changes in neurons (Anokhin, 1997). The c-fos expression is one of the inconsistency markers. The neurons acquiring their systemic specialization are selected from cells with c-fos expression (Svarnik, Anokhin, & Aleksandrov, 2001). At the behavioral level, individuals seek to eliminate situations of inconsistency by searching for solutions to problem situations through generating trial implementations of new behaviors. Achieving a useful result is a criterion for individuals' successful acquisition of new experience. In this case, a new element of individual experience is formed. This newly formed element joins the general structure; previously formed experience undergoes changes (Aleksandrov, 2005). The findings of numerous studies confirm the role of new elements of individual experience (McKenzie, Robinson, Herrera, Churchill, & Eichenbaum, 2013).

Some events make it impossible to find new ways to achieve a previous result. At that point, adaptation to new conditions (possibly due to modifications in the relations between elements of experience) becomes the only way to eliminate the inconsistency between needs and possibilities of achieving results. The concept of restriction embodies all the events that entail the impossibility of performing behaviors that previously led to the achievement of important results (due to the elimination of the object of interaction).We assume that the experience of adapting to restriction changes individual experience. This study aims to elucidate the characteristics of these changes in the structure of animal experience under restriction.

Currently, the studies on the extinction of instrumental skills are the most phenomenologically relevant to the problem of adapting to the impossibility of performing learned behavior. The studies on instrumental 'extinction' are based on the 'stimulus-response' methodology, which is different from the system-evolutionary methodology (Shvyrkov, 1995; Aleksandrov, 2005; *Alexandrov, 2018*). However, these studies address similar issues. In these works, researchers examine whether adaptation to the situation of the impossibility of performing the learned skills can be considered as learning, or it is rather the elimination of old inefficient models (Trask, Thrailkill, & Bouton, 2017; Todd, Vurbic, Bouton, 2014; Bouton, Trask, & Carranza-Jasso, 2016). Learning extinction is defined as process of acquiring a failure predicting skill.

Adaptation to such an undesirable situation as the impossibility of external performance of experience and the termination of inconsistency may be a result that replaces the previous result. Modification changes probably occur as an option, without acquiring a new element of experience, due to reconsolidation changes in associations among the already existing elements of experience.

The present study addresses expected changes in the structure of individual experience when the external performance of one of its elements is impossible. To investigate this issue, an attempt will now be made to identify and describe the behavioral characteristics and dynamics of neural activity during adaptation in terms of restriction.

We hypothesize that neurons that are active in previous experience may change their activity characteristics. Moreover, we assume that neurons associated with the preservation of behavior may also change their activity. In other words, neurons that are activated in certain behavioral act before and after restriction change their activity in terms of restriction.

Methods

The study was conducted on 7 adult Long-Evans rats (weight range 200 to 350 g). The animals were food-deprived during experimental sessions and trainings; weight loss was no more than 15% of their body weight. The experiments were performed in accordance with European Directive 86/609/EEC/11.24.1986 regulating the use of animals for experimental and other scientific purposes.

All the experiments were carried out in a special two-section cage (Fig. 1) bisected by a partition and equipped with photoelectric sensors for behavior control. The opposite angles (sides) of each section of the cage contained two feeders and two pedals. The feeders were placed at farthest corners of the cage, while the pedals were at the nearest ones. When the animals pressed the pedal, a special food tablet was automatically thrown into the feeder; the experimenter could also feed the tablet to the feeder by pressing a button.

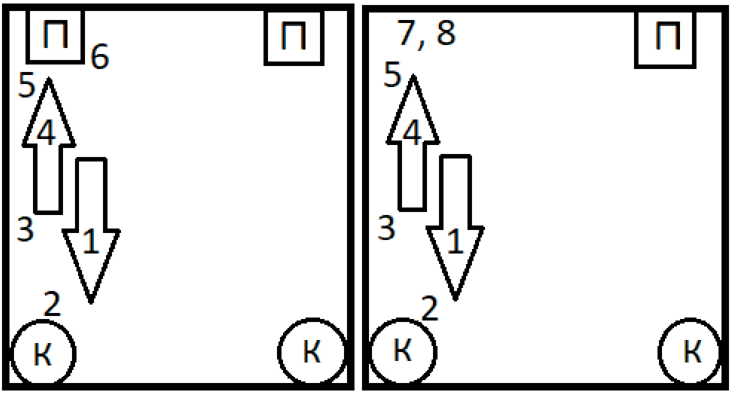


Figure 1.The experimental cage sections with 2 pedals (P) and 2 feeders (F)

Acts of instrumental food-seeking behavior: 1 – approaching the feeder; 2 – immersing the muzzle into the feeder; 3 – moving away from the feeder and approaching the pedal; 4 – passage through a partition; 5 – staying in the corner equipped with the pedal; 6 – pressing the pedal; as well as acts specific to restriction: 7 – sniffing the walls around the pedal; 8 – sniffing the holes in place of the removed pedal

Before the experiment sessions recording neural activity, we have carried out preliminary phased training in instrumental food-seeking behavior in rats. Within this training, we trained rats in food-seeking behavior at one side (pedal-feeder) of the cage. The training process was divided into 6 phases: approaching the feeder; immersing the muzzle into the feeder; moving away from the feeder and approaching the pedal; passing the partition; staying in the corner equipped with the pedal; pressing the pedal. During training sessions, the animals made 50-100 successful reinforced realizations of the corresponding acts of instrumental behavior. Certain acts (Fig. 1) constitute a cycle of instrumental food-seeking behavior (CIFB). Special attention was devoted to a specific act of food-seeking behavior – test immersing the muzzle into the feeder. An animal was considered to have learned behavior pattern if it performed independently more than 20 full cycles of instrumental food-seeking behavior.

After training we kept the animal in its home cage at rest for several days without restriction in food. The implantation of microelectrodes was then carried out under general anesthesia (Zoletil, Rometar). We scalped the animals, then trepanned them and installed manipulators above the place of registration of impulse activity corresponding to the localization of the retrosplenial cortex of the rat brain (P 5.0; L 0.5) (Paxinos, & Watson, 1997). Further, we lowered microelectrodes into the brain. We chose retrosplenial cortex to record neuronal activity. This could increase the likelihood of recording the activity of neurons specialized in instrumental food-seeking behavior based on previous studies (Gorkin, Kuzina, Ivlieva, Solovyova, & Aleksandrov, 2017; Kuzina, Gorkin, & Aleksandrov, 2015; Shevchenko, Aleksandrov, Gavrilov, Gorkin, & Grinchenko, 1986).

During the experiment, impulse signal from the electrodes passed through a signal amplifier (gain 3000, bandwidth 100 Hz – 2 kHz) (Gorkin, 2011), and then it was sent to the computer device, where the Discovery program (DataWaveTechnologies, USA) was used to record data from the tetrode. Besides, we used the photoelectric method to record the behavioral marks of pedal pressing, passing the partition and immersing the muzzle into the feeder. Thus, both spike activity of neurons and reference marks of behavior were recorded by the Discovery in a single file, with a single reference point, which allowed us to accurately compare individuals' behavior with their neural activity.

Further, we recorded the activity of retrosplenial cortical neurons in the behavioral cycles of animal food seeking on the side of the cage where the training took place. Then the experimenter turned off the working pedal, which pressing became ineffective. At that moment, we turned on the second pedal (on the other side of the cage); the animal had to learn how to press it. After training (the criterion was an average of 20 pressures), the experimenter switched the effectiveness of pedals; the first one became effective again, and so on (20 pressures for each pedal). After several sessions of pressing both pedals in turn, we removed the first one from the cage; a hole remained in its place, while the second pedal was untouched and remained in the 'alternating efficiency' mode (ineffective when we removed the first pedal). Thus, the animal found itself in a situation of impossibility to implement behavior – restriction. The animal stayed in terms of restriction for 5 minutes (average implementation time of 20 successful food-seeking behavioral act), after which another pedal became effective. After 20 successful pressures of the 'preserved pedal, the experimenter turned off its effectiveness. The animal was in terms of restriction again. In each session, we registered 2-3 restrictions alternating with successful behaviors on the other side of the cage. During all the experimental sessions, we recorded videos of the behavior of the animals and all the key moments of the sessions.

We distinguished the recorded multicellular activity from artifact signals and then divided them into separate clusters according to the signal amplitude at different electrodes. The resulting activity of individual neurons was compared with the behavior of individuals using the NeuRu program (A.K. Krylov). On the side of the cage, where we restricted the implementation of the behavioral act, we identified certain acts of food-seeking behavior, orientation, grooming and other forms of behavior as well as modified acts of behavior.

We were interested in the activity of neurons specialized in the behavioral acts identified by us (the 100% probability of activation in a particular act corresponds to 'specific' activity), as well as the neurons with not determined specialization but which were active in instrumental food-seeking behavior. If it was impossible to establish the association between the activation of a neuron and certain acts of behavior, or if activation of a neuron was not observed in the studied food-seeking behavior, we considered such cells as 'nonspecifically active'. In other words, they were considered as specialized in other forms of behavior formed irrespectively our trainings (Aleksandrov et al., 2014). Among these cells we distinguished those ones the probability of activating which reached more than 40–50% during the performance of one or more successive acts. We suggest that such neurons may be specialized in other behaviors, but are indirectly involved in ensuring the realization of this food-seeking behavior. Thus, for further statistical analysis we selected all the cells the probability of activating which was above 50%; we analyzed specialized cells additionally.

Using the NeuRu program, we obtained the activation frequency of individual cells for each implementation of behavioral acts. We carried out a statistical comparison between activation frequencies in acts of a successful food-seeking behavior before restriction and the acts of behavior when it was impossible to implement instrumental food-seeking behavior according to the Wilcoxon criterion; after obtaining significant differences, we analyzed the direction of changes. Similarly, we carried out a statistical comparison by food-seeking behavior at the other side of the experimental cage before and after restriction ("preserved" behavior) and for acts of other behaviors.

Results

The experiment with registration of neural activity was conducted on 7 adult Long-Evans rats. For some animals (4 rats), after a long restriction (several days, and accordingly, experimental sessions) we held a 'return' session – returning the previously removed pedal and reactivating its effectiveness. Further, 2 animals were subjected to restriction, when the second pedal was removed from the experimental cage.

The existing knowledge of the behavior of different animals in terms of prohobition enabled us to identify the most common specific acts that that were associated with the modified ineffective instrumental food-seeking behavior: approaching the hole in place of the removed pedal, finding the removed pedal in the corner, sniffing the hole, sniffing the corner in place of the removed pedal, approaching the feeder, immersing the muzzle into the feeder, passage through a partition (Chistova, Ivlieva, & Gorkin, 2018).

These behavioral acts could be compared with the acts of successful instrumental behavior. They were either similar to the acts of successful food-seeking behavior, or took place in the same place of the experimental cage. When comparing behavior parameters and neural activity we examined only the acts which were performed 3 times at least. We should note that in terms of restriction animals performed a fragmented cycle of instrumental food-seeking behavior; for example, after finding the pedal in the corner of the cage, they extremely rarely approach to the feeders. This indirectly indicates that changes occur when it is impossible to perform an element of individual experience in the integral structure of experience.

During the restriction sessions, we observed other forms of behavior including acts of grooming, which were predominantly performed by the animal near the hole in place of the removed pedal, and acts of orienting and exploring behavior (standings, sniffing of the cage). We observed a general decrease in the frequency of performing food-seeking behavior in terms of restriction (Mann–Whitney test, p <0.05), a decrease in the duration of these performances (Mann–Whitney test, p <0.05), and also a change in the ratio of the number of performed food-seeking behaviors and other forms of behavior (see Fig. 2).

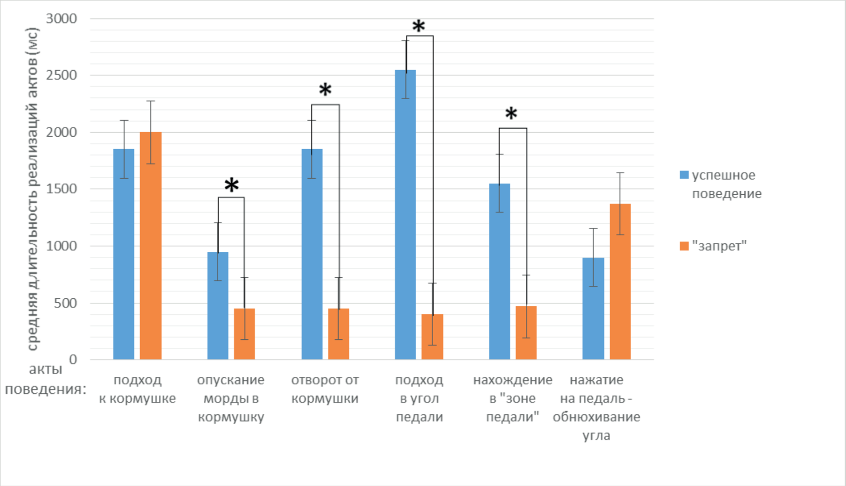


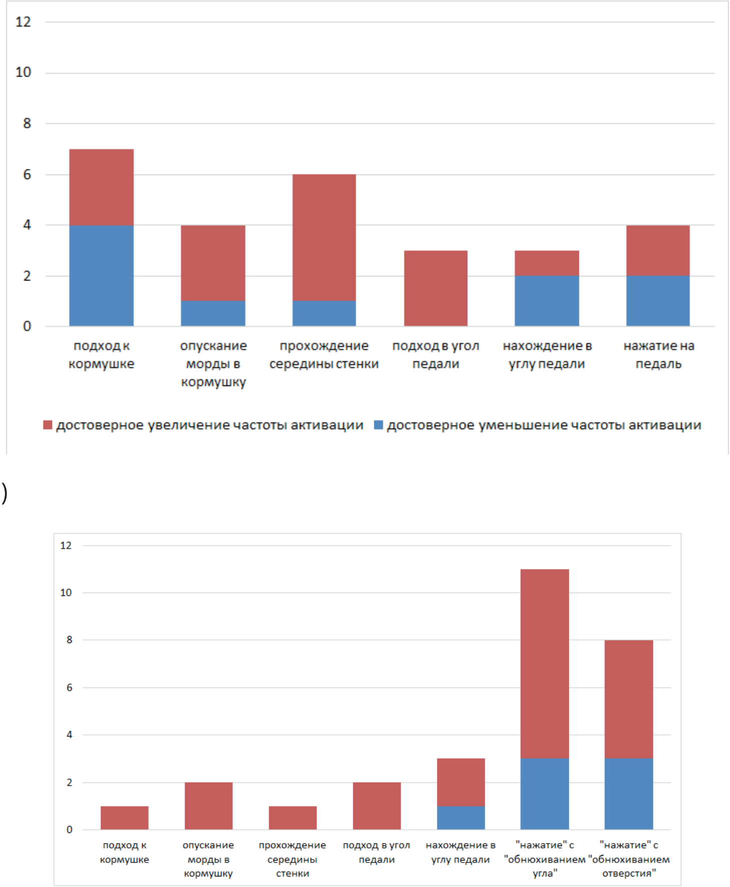
Figure 2. Comparing the average durations (ms) of performing successful food-seeking (in blue colour) and modified acts after removing the pedal (in orange colour)

Values represent the means ± standard errors. Asterisks indicate significant differences by the Mann–Whitney test (p < 0.05)

According to the Mann-Whitney criterion, the frequency of acts of orientating and exploring behavior (standings) turned out to be less significantly less ($p < 0.05$) in definitive behavior (the frequency of performing acts was 0.60 ± 0.15per minute) than in terms of restriction (frequency of performing acts was 0.15 ± 0.05). Meanwhile, the mean time for performing such acts in terms of restriction has not changed. Besides, after restriction the frequency and average duration of grooming acts did not change.

To control the changelessness of the position of the recording electrodes, we compared the activity of a population of neurons recorded from an individual animal's cortex before and after the procedure of pedal removing during the performance of various forms of behavior in that part of the experimental cage where the animal was placed at the beginning and the end of the experimental session. After comparing the general population activity using the Wilcoxon statistical criterion, in 7of 9 cases (restriction session) the average frequency of the activity of neuronal population did not significantly change ($p > 0.05$); 2 cases of a significant decrease in general population activity were excluded from the comparative analysis of neural activity in terms of restriction.

In the recorded multicellular activity we distinguished 30 patterns of activity of individual neurons. Meanwhile, we observed no specialized acts of food-seeking behavior in the experimental cage. We analyzed the activity of registered neurons during the performance of modified acts in terms of restriction. The number of acts performed was insufficient for the act-by-act statistical comparison in one animal (for 4 neurons). The analysis of the average frequency of neuronal activity, when the animal subjected to restriction, did not reveal significant changes compared with the activity of neurons during the performance of definitive behavior. The act-by-act statistical comparison showed that 15 of 26 neurons significantly changed the frequency of activity in at least a single act in terms of restriction (Fig. 3) (Mann-Whitney test, $p < 0.05$). Moreover, the greatest number of changes was observed in the following pairs of compared acts: successful pedal pressing / sniffing the walls in place of the removed pedal; successful pedal pressing / sniffing the holes in the removed pedal (11 and 8, respectively). All significant changes in the frequency of impulse activity were unidirectional in the context of belonging to a single neuron. In other words, the frequency of activity of an individual neuron either decreased or increased, with the decrease in the frequency of activity observing only in acts associated with the pedal removed ('approaching the corner', 'sniffing the corner', and 'sniffing holes').



(a)

(b)

Figure 3. Histograms of the number of neural activity patterns with a significant change in the frequency of activity in terms of prohibition

Distribution of the number of significant differences in the activity of individual neurons in the acts of:
(a) The food-seeking cycle preserved its efficiency: approaching the feeder – 7 neurons; immersing the muzzle into the feeder – 4 neurons; passage through a partition – 6 neurons; finding the pedal in the corner – 3 neurons; pressing the pedal – 4 neurons.
(b) The modified food-seeking behavior: approaching the feeder – 1 neuron; immersing the muzzle into the feeder – 2 neurons; passage through a partition wall – 1 neuron; approaching the pedal – 2 neurons; finding the pedal in the corner – 3 neurons.
Comparing the frequency of activity in 'pressing the pedal' and 'sniffing the corner in the zone of the pedal' – 11 neurons.
Comparing the frequency of activity in 'pressing the pedal' and 'sniffing the holes' – 8 neurons.

We discovered the neurons that were active in behavior in the part of the cage not subjected to restriction (in preserved behavior); these neurons changed their activity in terms of restriction. A more detailed analysis of the "preserved" instrumental food-seeking behavior was carried out for individual neural activity patterns. The act-by-act statistical comparison (the Mann–Whitney criterion) showed that the frequency of activity of 14 neurons during the performance of "preserved" behavior did not significantly change after the animal was subjected to restriction ($p > 0.05$). We observed significant changes in individual acts of behavior preserved its effectiveness in the activity of 16 neurons($p < 0.05$): in approaching the feeder – 7 neurons; immersing the muzzle into the feeder – 4 neurons; passage through a partition – 6 neurons; approaching the pedal – 3 neurons; finding the pedal in the corner – 3 neurons; pressing the pedal – 4 neurons. Significant changes in the frequencies of neuronal activity in the acts of preserved behavior (compared to these acts before restriction were multidirectional in the general population, exhibiting both the increase and the decrease in frequencies (Fig. 3). However in 15 of 16 neurons the frequency of activity of individual cells changed unidirectionally.

Thus, we may argue that restriction of on the performance the behavioral cycle in one part of the cage changes neuronal activity during the implementation of the behavior that has preserved its effectiveness. We now may assume that in this situation the greatest changes in the structure of individual experience are associated with the expectation of a result at the stage that immediately precedes the consummate act.

Discussion

In the experiments, we observed significant changes in the activity of neurons, which speaks in favor of modifications in the structure of individual experience, associated with the impossibility of "external" performance of one of its elements.

We found multidirectional significant differences in the frequency of activity of neurons during animals' performance of acts in the 'pedal zone' before and after its removal. The most part of the neurons that changed their activity in the restricted side increased the frequency of activation. The neurons that decreased their activity also showed a very low frequency before restriction. The decrease in their activity may be explained by the lack of behavior in which these cells showed non-specific activation. For the most part of cells the increase in the frequency of activity that changed their activity in the 'pedal zone' is presumably associated with inconsistency and the attempts to eliminate it. We also observed an increase in the number of standings in terms of restriction compared with the sessions of definitive behavior. As an indicator of orientating and exploring behavior standings may indicate a prolonged inconsistency experienced by the individual in terms of restriction. We assume that if trial acts and food-seeking behavior do not lead to finding new ways to achieve a result, inconsistency is prolonged. This prolonged inconsistency does not eliminate the contradiction between the metabolic ‘needs’ of the neuron and the real environment; death genes can be expressed in neurons, which lead to programmed cell death – apoptosis of neurons (Aleksandrov, 2004). Neuron death is a necessary condition for the formation of individual experience “when the metabolic needs of a neuron come into fatal contradiction with new ways of coordinating the needs of individual cells” (Aleksandrov, 2005, p. 853–855). In terms of restriction some cells with the increased activity may subsequently undergo apoptosis as part of general changes in the structure of experiment.

We discovered that the neurons that were nonspecifically activated in the ‘preserved behavior’ changed their activity (compared to the same behavior before restriction), mainly in result-oriented acts (approaching the feeder, checking, etc.). Thus, in terms of restriction the behavioral cycle in one side of the cage changes the activity of neurons during the performance of acts that have preserved their effectiveness in behavior, and, accordingly, restructuring the structure of individual experience. To some extent, this effect is similar to the process of accommodative reconsolidation of the elements of previously formed experience during the formation of a new element of experience in learning processes (Alexandrov et al., 2018).

Despite the changes in the structure of individual experience when performance is restricted, this element of experience still remains. The sessions with the return of the previously removed pedal when the animals resumed their food-seeking behavior clearly demonstrate this. The studies in the restoration of instrumental food-seeking behavior after its ‘extinction’ (Trask et al., 2017) demonstrate that there is no ‘erasure’ of the extinguished experience. It is shown that when conducting a test session in the context opposite to the ‘extinction’ session, the behavior is restored. This resumption of behavior is considered as ‘renewal’ (Bouton & Bolles, 1979). In the AAB renewal studies the formation of the ‘fear reaction’ takes place in the context of A; ‘extinction’ – in the context of B; the test session – in the context of A (Bouton & Bolles, 1979; Bouton & King, 1983; Bouton & Peck, 1989). In the ABC renewal studies, the final testing takes place in the new context of C (Bouton & King, 1983; Bouton & Ricker, 1994). Besides, some studies describe the AAB renewal, formation, and ‘extinction’ in the context of A; the test session – in the new context of B (Thomas, Larsen, & Ayres, 2003; Laborda, Witnauer, & Miller, 2011; Tamai & Nakajima, 2000). All three options of extinction – renewal experiments were also carried out for instrumental behavior (Bouton, Todd, Vurbic, & Winterbauer, 2011; Todd, 2013).

These experiments showed that the 'extinction' of instrumental behavior does not 'erase' the initial learning.

Considering the importance of the data obtained for understanding the processes of adaptation to prohibition in humans, we should note that the results of recent studies of the possibilities and mechanisms of influence on the formed memory in animals (without the use of pharmacological agents) play an important role in developing innovative approaches to 'editing' and depressing human memory, especially traumatic memory and memory related to post-traumatic stress disorders) (Phelps & Hofmann, 2019).

***Conclusions**:*

Changes in the frequency of neuronal activity in terms of restriction are mainly associated with the loss of the ability to perform a result-oriented behavioral act. This speaks in favor the changes in the structure of individual experience, directly related to the impossibility of 'external' performance of one of its elements.

Changes in the activity of neurons in preserved behavior bring evidence for modifications affected not only the element of experience directly subjected to restriction but also the element associated with it, which do not contradicts to the concept of adaptive reconsolidation of experience.

In most cases the increase in the frequency of activity of neurons, changes in their activity, as well as certain behavioral parameters (i.e. the highest frequency of grooming in place of the removed pedal, an increase in the number of standings in terms of restriction) indicates a prolonged discoordination. Discoordination leads to changes in the structure of individual experience associated with both morphological and functional modifications of neurons and perhaps with the death of some neurons.

The experiments aimed at identifying the mechanisms influencing the formed memory in animals play an important role not only for basic research on the dynamics of human memory, but also for developing approaches to 'editing' memory.

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